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BENZOTHIAZINONE AND BENZOXAZINONE COMPOUNDS

RELATED APPLICATION(S)

This application claims the benefit of U.S. Provisional Application No.: 60/137,410, filed June 3, 1999, the entire teachings of which are incorporated herein by reference.

This invention relates to certain benzothiazinones and benzoxazinones which are inhibitors of protein kinases, particularly tyrosine kinases and serine/threonine kinases, of which some are novel compounds, to pharmaceutical compositions containing these benzothiazinones or benzoxazinones, and to processes for preparing these benzothiazinones and benzoxazinones.

BACKGROUND OF THE INVENTION

There are at least 400 enzymes identified as protein kinases. These enzymes catalyze the phosphorylation of target protein substrates. The phosphorylation is usually a transfer reaction of a phosphate group from ATP to the protein substrate. The specific structure in the target substrate to which the phosphate is transferred is a tyrosine, serine or threonine residue. Since these amino acid residues are the target structures for the

phosphoryl transfer, these protein kinase enzymes are commonly referred to as tyrosine kinases or serine/threonine kinases.

The phosphorylation reactions, and counteracting phosphatase reactions, at the tyrosine, serine and threonine residues are involved in countless cellular processes that underlie responses to diverse intracellular signals (typically mediated through cellular receptors), regulation of cellular functions, and activation or deactivation of cellular processes. A cascade of protein kinases often participate in intracellular signal transduction and are necessary for the realization of these cellular processes. Because of their ubiquity in these processes, the protein kinases can be found as an integral part of the plasma membrane or as cytoplasmic enzymes or localized in the nucleus, often as components of enzyme complexes. In many instances, these protein kinases are an essential element of enzyme and structural protein complexes that determine where and when a cellular process occurs within a cell.

Protein Tyrosine Kinases. Protein tyrosine kinases (PTKs) are enzymes which catalyse the phosphorylation of specific tyrosine residues in cellular proteins. This post-translational modification of these substrate proteins, often enzymes themselves, acts as a molecular switch regulating cell proliferation, activation or differentiation (for review, see Schlessinger and Ulrich, 1992, *Neuron* 9:383-391). Aberrant or excessive PTK activity has been observed in many disease states including benign and malignant proliferative disorders as well as diseases resulting from inappropriate activation of the immune system (e.g., autoimmune disorders), allograft rejection, and graft vs. host disease. In addition, endothelial-cell specific receptor PTKs such as KDR and Tie-2 mediate the angiogenic process, and are thus involved in supporting the progression of cancers and other diseases involving inappropriate vascularization (e.g., diabetic retinopathy, choroidal neovascularization due to age-related macular degeneration, psoriasis, arthritis, retinopathy of prematurity, infantile hemangiomas).

Tyrosine kinases can be of the receptor-type (having extracellular, transmembrane and intracellular domains) or the non-receptor type (being wholly intracellular).

Receptor Tyrosine Kinases (RTKs). The RTKs comprise a large family of transmembrane receptors with diverse biological activities. At present, at least nineteen (19) distinct RTK subfamilies have been identified. The receptor tyrosine kinase (RTK) family includes receptors that are crucial for the growth and differentiation of a variety of cell types (Yarden and Ullrich, *Ann. Rev. Biochem.* 57:433-478, 1988; Ullrich and Schlessinger, *Cell* 61:243-254, 1990). The intrinsic function of RTKs is activated upon ligand binding, which results in phosphorylation of the receptor and multiple cellular substrates, and subsequently in a variety of cellular responses (Ullrich & Schlessinger, 1990, *Cell* 61:203-212). Thus, receptor tyrosine kinase mediated signal transduction is initiated by extracellular interaction with a specific growth factor (ligand), typically followed by receptor dimerization, stimulation of the intrinsic protein tyrosine kinase activity and receptor trans-phosphorylation. Binding sites are thereby created for intracellular signal transduction molecules and lead to the formation of complexes with a spectrum of cytoplasmic signaling molecules that facilitate the appropriate cellular response. (e.g., cell division, differentiation, metabolic effects, changes in the extracellular microenvironment) see Schlessinger and Ullrich, 1992, *Neuron* 9:1-20.

Proteins with SH2 (src homology -2) or phosphotyrosine binding (PTB) domains bind activated tyrosine kinase receptors and their substrates with high affinity to propagate signals into cell. Both of the domains recognize phosphotyrosine. (Fantl et al., 1992, *Cell* 69:413-423; Songyang et al., 1994, *Mol. Cell. Biol.* 14:2777-2785; Songyang et al., 1993, *Cell* 72:767-778; and Koch *et al.*, 1991, *Science* 252:668-678; Shoelson, *Curr. Opin. Chem. Biol.* (1997), 1(2), 227-234; Cowburn, *Curr. Opin. Struct. Biol.* (1997), 7(6), 835-838). Several intracellular substrate proteins that associate with receptor tyrosine kinases (RTKs) have been identified. They may be divided into two principal groups: (1) substrates which have a catalytic domain; and (2) substrates which

lack such a domain but serve as adapters and associate with catalytically active molecules (Songyang *et al.*, 1993, *Cell* 72:767-778). The specificity of the interactions between receptors or proteins and SH2 or PTB domains of their substrates is determined by the amino acid residues immediately surrounding the phosphorylated tyrosine residue. For example, differences in the binding affinities between SH2 domains and the amino acid sequences surrounding the phosphotyrosine residues on particular receptors correlate with the observed differences in their substrate phosphorylation profiles (Songyang *et al.*, 1993, *Cell* 72:767-778). Observations suggest that the function of each receptor tyrosine kinase is determined not only by its pattern of expression and ligand availability but also by the array of downstream signal transduction pathways that are activated by a particular receptor as well as the timing and duration of those stimuli. Thus, phosphorylation provides an important regulatory step which determines the selectivity of signaling pathways recruited by specific growth factor receptors, as well as differentiation factor receptors.

Several receptor tyrosine kinases, and growth factors that bind thereto, have been suggested to play a role in angiogenesis, although some may promote angiogenesis indirectly (Mustonen and Alitalo, *J. Cell Biol.* 129:895-898, 1995). One such receptor tyrosine kinase, known as "fetal liver kinase 1" (FLK-1), is a member of the type III subclass of RTKs. An alternative designation for human FLK-1 is "kinase insert domain-containing receptor" (KDR) (Terman *et al.*, *Oncogene* 6:1677-83, 1991). Another alternative designation for FLK-1/KDR is "vascular endothelial cell growth factor receptor 2" (VEGFR-2) since it binds VEGF with high affinity. The murine version of FLK-1/VEGFR-2 has also been called NYK (Oelrichs *et al*, *Oncogene* 8(1):11-15, 1993). DNAs encoding mouse, rat and human FLK-1 have been isolated, and the nucleotide and encoded amino acid sequences reported (Matthews *et al.*, *Proc. Natl. Acad. Sci.* USA, 88:9026-30, 1991; Terman *et al.*, 1991, *supra*; Terman *et al.*, *Biochem. Biophys. Res. Comm.* 187:1579-86, 1992; Sarzani *et al.*, *supra*; and Millauer *et al.*, *Cell* 72:835-846, 1993). Numerous studies such as those reported in Millauer *et al.*,

supra, suggest that VEGF and FLK-1/KDR/VEGFR-2 are a ligand-receptor pair that play an important role in the proliferation of vascular endothelial cells, and formation and sprouting of blood vessels, termed vasculogenesis and angiogenesis, respectively.

Another type III subclass RTK designated "fms-like tyrosine kinase-1" (Flt-1) is related to FLK-1/KDR (DeVries et al. *Science* 255;989-991, 1992; Shibuya et al., *Oncogene* 5:519-524, 1990). An alternative designation for Flt-1 is "vascular endothelial cell growth factor receptor 1" (VEGFR-1). To date, members of the FLK-1/ KDR/VEGFR-2 and Flt-1/ VEGFR-1 subfamilies have been found expressed primarily on endothelial cells. These subclass members are specifically stimulated by members of the vascular endothelial cell growth factor (VEGF) family of ligands (Klagsburn and D'Amore, *Cytokine & Growth Factor Reviews* 7: 259-270, 1996). Vascular endothelial cell growth factor (VEGF) binds to Flt-1 with higher affinity than to FLK-1/KDR and is mitogenic toward vascular endothelial cells (Terman et al., 1992, *supra*; Mustonen et al. *supra*; DeVries et al., *supra*). Flt-1 is believed to be essential for endothelial organization during vascular development. Flt-1 expression is associated with early vascular development in mouse embryos, and with neovascularization during wound healing (Mustonen and Alitalo, *supra*). Expression of Flt-1 in adult organs such as kidney glomeruli suggests an additional function for this receptor that is not related to cell growth (Mustonen and Alitalo, *supra*).

As previously stated, recent evidence suggests that VEGF plays a role in the stimulation of both normal and pathological angiogenesis (Jakeman *et al.*, *Endocrinology* 133: 848-859, 1993; Kolch *et al.*, *Breast Cancer Research and Treatment* 36: 139-155, 1995; Ferrara *et al.*, *Endocrine Reviews* 18(1); 4-25, 1997; Ferrara et al., Regulation of Angiogenesis (ed. L. D. Goldberg and E.M. Rosen), 209-232, 1997). In addition, VEGF has been implicated in the control and enhancement of vascular permeability (Connolly, *et al.*, *J. Biol. Chem.* 264: 20017-20024, 1989; Brown *et al.*, *Regulation of Angiogenesis* (ed. L.D. Goldberg and E.M. Rosen), 233-269, 1997).

Different forms of VEGF arising from alternative splicing of mRNA have been reported, including the four species described by Ferrara *et al.* (*J. Cell. Biochem.* 47:211-218, 1991). Both secreted and predominantly cell-associated species of VEGF have been identified by Ferrara *et al. supra*, and the protein is known to exist in the form of disulfide linked dimers.

Several related homologs of VEGF have recently been identified. However, their roles in normal physiological and disease processes have not yet been elucidated. In addition, the members of the VEGF family are often coexpressed with VEGF in a number of tissues and are, in general, capable of forming heterodimers with VEGF. This property likely alters the receptor specificity and biological effects of the heterodimers and further complicates the elucidation of their specific functions as illustrated below (Korpelainen and Alitalo, *Curr. Opin. Cell Biol.*, 159-164, 1998 and references cited therein).

Placenta growth factor (PlGF) has an amino acid sequence that exhibits significant homology to the VEGF sequence (Park *et al.*, *J. Biol. Chem.* 269:25646-54, 1994; Maglione *et al. Oncogene* 8:925-31, 1993). As with VEGF, different species of PlGF arise from alternative splicing of mRNA, and the protein exists in dimeric form (Park *et al.*, *supra*). PlGF-1 and PlGF-2 bind to Flt-1 with high affinity, and PlGF-2 also avidly binds to neuropilin-1 (Migdal *et al*, *J. Biol. Chem.* 273 (35): 22272-22278), but neither binds to FLK-1/KDR (Park *et al.*, *supra*). PlGF has been reported to potentiate both the vascular permeability and mitogenic effect of VEGF on endothelial cells when VEGF is present at low concentrations (purportedly due to heterodimer formation) (Park *et al.*, *supra*).

VEGF-B is produced as two isoforms (167 and 185 residues) that also appear to bind Flt-1/VEGFR-1. It may play a role in the regulation of extracellular matrix degradation, cell adhesion, and migration through modulation of the expression and activity of urokinase type plasminogen activator and plasminogen activator inhibitor 1 (Pepper *et al*, *Proc. Natl. Acad. Sci. U. S. A.* (1998), 95(20): 11709-11714).

VEGF-C was originally cloned as a ligand for VEGFR-3/Flt-4 which is primarily expressed by lymphatic endothelial cells. In its fully processed form, VEGF-C can also bind KDR/VEGFR-2 and stimulate proliferation and migration of endothelial cells *in vitro* and angiogenesis in *in vivo* models (Lymboussaki *et al*, *Am. J. Pathol.* (1998), 153(2): 395-403; Witzenbichler *et al*, *Am. J. Pathol.* (1998), 153(2), 381-394). The transgenic overexpression of VEGF-C causes proliferation and enlargement of only lymphatic vessels, while blood vessels are unaffected. Unlike VEGF, the expression of VEGF-C is not induced by hypoxia (Ristimaki *et al*, *J. Biol. Chem.* (1998), 273(14),8413-8418).

The most recently discovered VEGF-D is structurally very similar to VEGF-C. VEGF-D is reported to bind and activate at least two VEGFRs, VEGFR-3/Flt-4 and KDR/VEGFR-2. It was originally cloned as a c-fos inducible mitogen for fibroblasts and is most prominently expressed in the mesenchymal cells of the lung and skin (Achen *et al*, *Proc. Natl. Acad. Sci. U. S. A.* (1998), 95(2), 548-553 and references therein).

As for VEGF, VEGF-C and VEGF-D have been claimed to induce increases in vascular permeability *in vivo* in a Miles assay when injected into cutaneous tissue (PCT/US97/14696; WO98/07832, Witzenbichler *et al., supra*). The physiological role and significance of these ligands in modulating vascular hyperpermeability and endothelial responses in tissues where they are expressed remains uncertain.

Based upon emerging discoveries of other homologs of VEGF and VEGFRs and the precedents for ligand and receptor heterodimerization, the actions of such VEGF homologs may involve formation of VEGF ligand heterodimers, and/or heterodimerization of receptors, or binding to a yet undiscovered VEGFR (Witzenbichler *et al., supra*). Also, recent reports suggest neuropilin-1 (Migdal *et al, supra*) or VEGFR-3/Flt-4 (Witzenbichler *et al., supra*), or receptors other than KDR/VEGFR-2 may be involved in the induction of vascular permeability (Stacker, S.A., Vitali, A., Domagala, T., Nice, E., and Wilks, A.F., "Angiogenesis and Cancer" Conference, Amer. Assoc. Cancer Res., Jan. 1998, Orlando, FL; Williams, *Diabetelogia*

40: S118-120 (1997)). Until now, no direct evidence for the essential role of KDR in VEGF-mediated vascular hyperpermeability has been disclosed.

The Non-Receptor Tyrosine Kinases. The non-receptor tyrosine kinases represent a collection of cellular enzymes which lack extracellular and transmembrane sequences. At present, over twenty-four individual non-receptor tyrosine kinases, comprising eleven (11) subfamilies (Src, Frk, Btk, Csk, Abl, Zap70, Fes/Fps, Fak, Jak, Ack and LIMK) have been identified. At present, the Src subfamily of non-receptor tyrosine kinases is comprised of the largest number of PTKs and include Src, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr and Yrk. The Src subfamily of enzymes has been linked to oncogenesis. A more detailed discussion of non-receptor tyrosine kinases is provided in Bolen, 1993, *Oncogene* 8:2025-2031, which is incorporated herein by reference.

Many of the tyrosine kinases, whether an RTK or non-receptor tyrosine kinase, have been found to be involved in cellular signaling pathways involved in numerous pathogenic conditions, including cancer, psoriasis, and other hyperproliferative disorders or hyper-immune responses.

Development of Compounds to Modulate the PTKs. In view of the surmised importance of PTKs to the control, regulation, and modulation of cell proliferation, the diseases and disorders associated with abnormal cell proliferation, many attempts have been made to identify receptor and non-receptor tyrosine kinase "inhibitors" using a variety of approaches, including the use of mutant ligands (U.S. Application No. 4,966,849), soluble receptors and antibodies (Application No. WO 94/10202; Kendall & Thomas, 1994, *Proc. Natl. Acad. Sci* 90:10705-09; Kim *et al.*, 1993, *Nature* 362:841-844), RNA ligands (Jellinek, *et al.*, *Biochemistry* 33:10450-56; Takano, *et al.*, 1993, *Mol. Bio. Cell* 4:358A; Kinsella, *et al.* 1992, *Exp. Cell Res.* 199:56-62; Wright, *et al.*, 1992, *J. Cellular Phys.* 152:448-57) and tyrosine kinase inhibitors (WO 94/03427; WO 92/21660; WO 91/15495; WO 94/14808; U.S. Patent No. 5,330,992; Mariani, *et al.*, 1994, *Proc. Am. Assoc. Cancer Res.* 35:2268).

More recently, attempts have been made to identify small molecules which act as tyrosine kinase inhibitors. For example, bis monocyclic, bicyclic or heterocyclic aryl compounds (PCT WO 92/20642) and vinylene-azaindole derivatives (PCT WO 94/14808) have been described generally as tyrosine kinase inhibitors. Styryl compounds (U.S. Patent No. 5,217,999), styryl-substituted pyridyl compounds (U.S. Patent No. 5,302,606), certain quinazoline derivatives (EP Application No. 0 566 266 A1; *Expert Opin. Ther. Pat.* (1998), 8(4): 475-478), selenoindoles and selenides (PCT WO 94/03427), tricyclic polyhydroxylic compounds (PCT WO 92/21660) and benzylphosphonic acid compounds (PCT WO 91/15495) have been described as compounds for use as tyrosine kinase inhibitors for use in the treatment of cancer. Anilinocinnolines (PCT WO97/34876) and quinazoline derivative compounds (PCT WO97/22596; PCT WO97/42187) have been described as inhibitors of angiogenesis and vascular permeability.

In addition, attempts have been made to identify small molecules which act as serine/threonine kinase inhibitors. For example, bis(indolylmaleimide) compounds have been described as inhibiting particular PKC serine/threonine kinase isoforms whose signal transducing function is associated with altered vascular permeability in VEGF-related diseases (PCT WO97/40830; PCT WO97/40831).

Plk-1 Kinase Inhibitors

Plk-1 is a serine/threonine kinase which is an important regulator of cell cycle progression. It plays critical roles in the assembly and the dynamic function of the mitotic spindle apparatus. Plk-1 and related kinases have also been shown to be closely involved in the activation and inactivation of other cell cycle regulators, such as cyclin-dependent kinases. High levels of Plk-1 expression are associated with cell proliferation activities. It is often found in malignant tumors of various origins. Inhibitors of Plk-1 are expected to block cancer cell proliferation by disrupting processes involving mitotic spindles and inappropriately activated cyclin-dependent kinases.

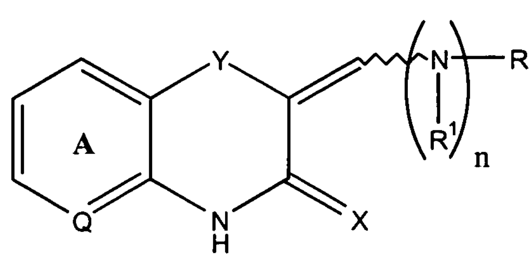
Cdc2/Cyclin B Kinase Inhibitors (Cdc2 is also known as cdk1)

Cdc2/cyclin B is another serine/threonine kinase enzyme which belongs to the cyclin-dependent kinase (cdks) family. These enzymes are involved in the critical transition between various phases of cell cycle progression. It is believed that uncontrolled cell proliferation, which is the hallmark of cancer is dependent upon elevated cdk activities in these cells. The inhibition of elevated cdk activities in cancer cells by cdc2/cyclin B kinase inhibitors could suppress proliferation and may restore the normal control of cell cycle progression.

The identification of effective small compounds which specifically inhibit signal transduction and cellular proliferation by modulating the activity of receptor and non-receptor tyrosine and serine/threonine kinases to regulate and modulate abnormal or inappropriate cell proliferation, differentiation, or metabolism is therefore desirable. In particular, the identification of methods and compounds that specifically inhibit the function of a tyrosine kinase which is essential for angiogenic processes or the formation of vascular hyperpermeability leading to edema, ascites, effusions, exudates, and macromolecular extravasation and matrix deposition as well as associated disorders would be beneficial.

SUMMARY OF THE INVENTION

This invention is directed to compounds of the formula



I.

and physiologically acceptable salts thereof, wherein, ring A is substituted or unsubstituted; Q is -N= or -CR^2=; X is S, O, or NOR^3; Y is -O-, -S-, -SO- or -SO$_2$-; R and R^1 are each, independently, hydrogen, a substituted or unsubstituted aliphatic, aromatic, heteroaromatic or aralkyl group; R^2 is hydrogen or a substituent; R^3 is

hydrogen or -C(O)R^4; R^4 is a substituted or unsubstituted aliphatic or aromatic group; and n is an integer from 0 to 1.

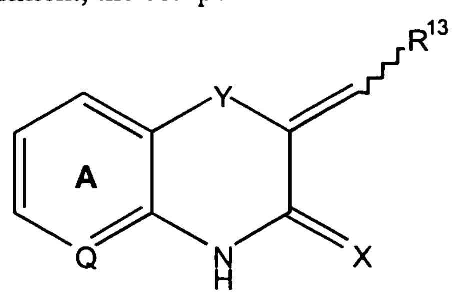
Aliphatic groups include straight chained or branched C_1-C_{18} hydrocarbons, or cyclic C_3-C_{18} hydrocarbons which are completely saturated or which contain one or more units of unsaturation. Lower alkyl groups are straight chained or branched C_1-C_6 hydrocarbons or C_3-C_6 cyclic hydrocarbons, which are completely saturated.

Aromatic groups include carbocyclic ring systems (e.g. benzyl and cinnamyl) and fused polycyclic aromatic ring systems (e.g. naphthyl and 1,2,3,4-tetrahydronaphthyl). In addition, aromatic groups includes heteroaryl ring systems (e.g. pyridines, thiophenes, furans, pyrroles, imidazoles, pyrazoles, triazoles, pyrimidines, pyrazines, pyridazines, oxazoles, thiazoles, isoxazoles, isothiazoles, tetrazoles, oxadiazoles, or thiadiazoles) and heteroaryl ring systems in which a carbocyclic aromatic ring, carbocyclic non-aromatic ring or heteroaryl ring is fused to one or more other heteroaryl rings (e.g. benzimidazole, indole, tetrahydroindole, azaindole, indazole, quinoline, imidazopyridine, purine, pyrrolo[2,3-d]pyrimidine, pyrazolo[3,4-d]pyrimidine) and their N-oxides. An aryl group, as used herein, refer to an aromatic group having five or six atoms. An aralkyl group is an aryl substituent that is linked to a compound by an aliphatic group having from one to about six carbon atoms. Similarly, a heteroaralkyl group is a heteroaryl moiety that is linked to a compound by an aliphatic group having from one to about six carbon atoms; and a heterocycloalkyl group is a heteroaryl moiety that is linked to a compound by an aliphatic group having from one to about six carbon atoms.

Suitable substituents include halogens, trihalomethyl, cyano, hydroxy, nitro, -$NR^5 R^6$, carbamoyl, carboxy, carboxamidoxime, -$SO_2NR^5R^6$, -$NHSO_2R^5$, R^7-O-R^8- or R^7-O-R^8-O-R^9-, wherein R^5 and R^6 are each, independently, hydrogen, a lower alkyl, benzyl, heteroarylmethyl or aryl group optionally substituted with a halogen, cyano or hydroxy group; R^7 is hydrogen, R^{10}C(O)-, or a lower alkyl or aryl group which is optionally substituted with one or more halogens, cyano, hydroxy or -NR^5R^6; R^8 and R^9

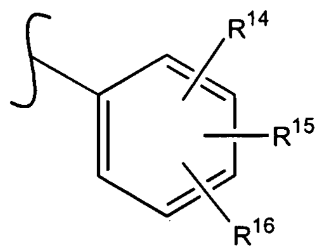
are each, independently, -C(O)- or a lower alkyl or aryl group which is optionally substituted with one or more halogens, cyano, hydroxy or $-NR^5R^6$; and R^{10} is a lower alkyl or an aryl group. Other suitable substitutents include R^{11}-, R^{11}O-, R^{11}OC(O)-, R^{11}NHC(O)-, R^{11}C(O)-, R^{11}C(O)O-, R^{11}S-, R^{11}S(O)-, $R^{11}S(O)_2$-, R^5R^6NC(O)-, R^{11}HNC(O)NH-, R^{11}C(O)NH-, $R^{12}(CH_2)_m$-, $R^{12}(CH_2)_m$ C(O)NH-, $R^{12}(CH_2)_m$O-, $R^{12}(CH_2)_m$NH-, $[R^{12}(CH_2)_m]_2$CH-O-$(CH_2)_m$-, $R^{12}(CH_2)_m$OC(O)-, $R^{12}(CH_2)_m$NHC(O)-, $R^{12}(CH_2)_m$CH(R^{12})$(CH_2)_m$-, $R^{12}(CH_2)_m$C(O)O-, $R^{12}(CH_2)_m$NHC(O)O-, $R^{12}(CH_2)_m$OC(O)NH-, $R^{12}(CH_2)_m$OC(O)O-, $R^{12}(CH_2)_m$NHC(O)$(CH_2)_m$-, $R^{12}(CH_2)_m$OC(O)$(CH_2)_m$-, $R^{12}(CH_2)_m(CR^5R^6)_m(CH_2)_m$N($R^5$)$(CH_2)_m$-, R^{12}C(O)$(CH_2)_m$-, $R^{12}(CH_2)_m(CR^5R^6)_m(CH_2)_m$N($R^5$)C(O)$(CH_2)_m$-, $R^{12}(CH_2)_m(CR^5R^6)_m(CH_2)_m$N($R^5$)$(CH_2)_m$C(O)-, $[R^{12}(CH_2)_m]_2$NC(O)$(CH_2)_m$-, $R^{12}(CH_2)_m$C(O)-, , $R^{12}(CH_2)_m(CR^5R^6)_m(CH_2)_m$N($R^5$)$SO_2$-, $R^{12}(CH_2)_m(CR^5R^6)_m(CH_2)_mO(CH_2)_m$-, wherein R^{11} is hydrogen, a lower alkyl group, a saturated or unsaturated heterocyclic ring, an aryl group or an aralkyl group where these groups are optionally substituted with one or more halogens, cyano, hydroxy or $-NR^5R^6$; R^{12} is halogen, carboxy, carbamoyl, lower alkyloxycarbonyl, lower alkenyl, hydroxy, a lower alkyloxy, a lower alcanoyloxy, $-NR^5R^6$ or is selected from the group consisting of morpholine, piperazine, piperidine, pyrrolidine, homopiperazine, pyridine, triazole, tetrazole, imidazole and tetrahydropyrane optionally substituted with an hydroxy, lower alkyl, lower alkyloxy, lower hydroxyalkyl, lower aminoalkyl, lower alkyloxyalkyl, a saturated or unsaturated heterocyclic ring, cycloalkyl or $-NR^5R^6$ group; and m is independently an integer from 0 to 4. Specific compounds of formula I are given in List I.

In one embodiment, the compounds of the invention are represented by the formula



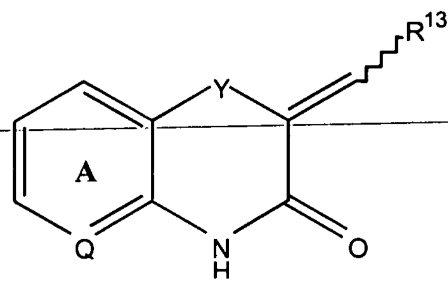
II.

and physiologically acceptable salts thereof, wherein ring A is substituted or unsubstituted, and Q, X, and Y are defined as above. R^{13} is hydrogen, a substituted or unsubstituted aliphatic group, a substituted or unsubstituted heteroaryl or a group represented by the following structure:



wherein, R^{14}, R^{15} and R^{16} are, independently, an alkyl, hydrogen, halogen, hydroxyl, thiol, thioether, $-NR^5R^6$, aldehyde, carboxylic acid or amide, with the proviso that R^{13} is not 3-furanyl, thiophenyl or 3-pyridinyl.

In another embodiment, the compounds of the invention are represented by the formula

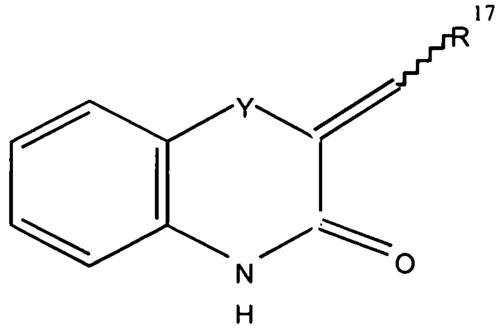


III.

and physiologically acceptable salts thereof, wherein ring A is substituted or unsubstituted, and Q, Y and R^{13} are defined as above.

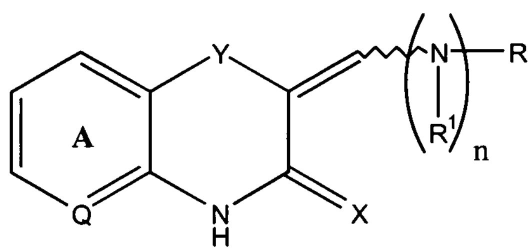
In a preferred embodiment the compounds of the invention are represented by the following formula;

IV.



and physiologically acceptable salts thereof, wherein Y is –0- or -S- and R^{17} is substituted or unsubstituted pyrrole, pyrazole, imidazole, oxazole, isoxazole, thiazole, isothiazole, triazole, tetrazole, indole, 7-azaindole, indazole, purine, pyrrolo[2,3-d]pyrimidine, pyrazolo[3,4-d]pyrimidine, imidazo[4,5-b] pyridine, imidazo[1,2-a] pyrimidine, imidazo[1,2-a]pyridine, pyrrolo[3,2-b] pyridine, pyrrolo[3,2-c] pyridine, pyrrolo[3,2-b]quinoline or pyrrolo[2,3-b]pyrazine.

In another aspect, the present invention is directed to a method of inhibiting one or more protein kinase activity comprising the administration of a compound represented by the formula:



Ia.

and physiologically acceptable salts thereof, wherein:

ring A is substituted or unsubstituted;

Q is -N= or $-CR^2=$;

X is S, O, or NOR^3;

Y is -O-, -S-, -SO- or $-SO_2-$;

R and R^1 are each, independently, hydrogen or a substituted or unsubstituted aliphatic, aromatic, or aralkyl group;

R^2 is -H or a substitutent;

R^3 is -H or $-C(O)R^4$;

R^4 is a substituted or unsubstituted aliphatic, aromatic, or aralkyl group; and

n is an integer from 0 to 1.

A preferred method of the immediately foregoing method is where the compound is a mixture of stereoisomers.

A preferred method of the immediately foregoing method is where the stereoisomers are enantiomers.

A preferred method of the immediately foregoing method is where the stereoisomers are E and Z isomers.

A preferred method of any of the foregoing methods is where the compound is a mixture of structural isomers.

A preferred method of the immediately foregoing method is where the structural isomers are tautomers.

A preferred method of any of the foregoing methods is where said protein kinase is either a receptor tyrosine kinase or a non-receptor tyrosine kinase.

A preferred method of the immediately foregoing method is where said tyrosine kinase is selected from the group consisting of KDR, flt-1, TIE-2, Lck, Src, fyn, Lyn, Blk, and yes.

In another aspect the present invention is directed to a method of treating a hyperproliferative disorder in a recipient which comprises administering to said recipient an effective amount of a compound of formula Ia or a physiologically acceptable salt thereof.

In another aspect the present invention is directed to a method of affecting angiogenesis in a recipient which comprises administering to said recipient an effective amount of a compound of formula Ia or a physiologically acceptable salt thereof. Preferred is where the angiogenesis affect in said recipient is an anti-angiogenic affect.

In another aspect, the present invention is directed to a method of treating a disease in a mammal in need thereof, wherein said disease is selected from the group consisting of cancer, arthritis, atherosclerosis, psoriasis, hemangioma, myocardial angiogenesis, coronary and cerebral collateral vascularization, ischemic limb angiogenesis, corneal disease, rubeosis, neovascular glaucoma, macular degeneration,

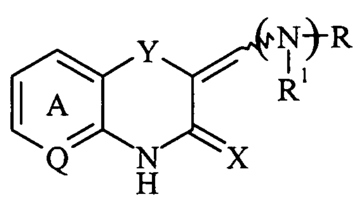
retinopathy of prematurity, wound healing, ulcers, *Helicobacter* related diseases, fractures, endometriosis, diabetic retinopathy, cat scratch fever, thyroid hyperplasia, burns, trauma, acute lung injury, chronic lung disease, stroke, polyps, cysts, synovitis, chronic and allergic inflammation, ovarian hyperstimulation syndrome, pulmonary and cerebral edema, keloid, fibrosis, cirrhosis, carpal tunnel syndrome, sepsis, adult respiratory distress syndrome, multiple-organ dysfunction syndrome, ascites and tumor-associated effusions and edema, comprising the step of administering a compound of formula Ia as described hereinabove or a physiologically acceptable salt thereof.

In another aspect, the present invention is directed to a method of inhibiting vascular hyperpermeability or the production of edema in a recipient which comprises administering to said recipient an effective amount of a compound of formula Ia or physiologically acceptable salts thereof.

A preferred method of any of the foregoing methods is where said protein kinase is a serine kinase.

A preferred method of any of the foregoing methods is where said protein kinase is a threonine kinase.

In yet another aspect, the present invention provides a compound represented by the following structural formula:



Ib.

and physiologically acceptable salts thereof, wherein:

ring A is substituted or unsubstituted;

Q is -N= or $-CR^2=$;

X is S, O, or NOR^3;

Y is -O-, -S-, -SO- or $-SO_2-$;

R^2 is -H or a substituent;

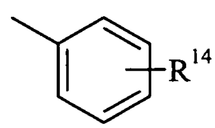
R^3 is -H or $-C(O)R^4$;

R^4 is a substituted or unsubstituted aliphatic or aromatic group;

n is 0 or 1;

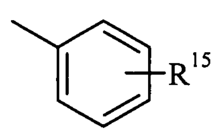
when X is S or NOR^3, R is a substituted or unsubstituted aromatic or aralkyl group and R^1 is hydrogen or a substituted or unsubstituted aliphatic group;

when X is O and n is 0, R^1 is hydrogen or a substituted or unsubstituted aliphatic group and R is a substituted or unsubstituted aromatic or aralkyl group, provided that R is not thiophenyl, benzoxadiazolyl, 3-furanyl, 3-pyridinyl or



where R^{14} is H, CF_3, phenyl, $-OCH_3$, -O-phenyl, NO_2 or $-OC(O)CH_3$; and

when X is O and n is 1, R^1 is H or a substituted or unsubstituted aliphatic group and R is a substituted or unsubstituted aromatic or aralkyl group, provided that R is not



where R^{15} is H, Cl, CH_3 or CF_3.

A preferred compound of formula Ib is where the aromatic group and the aromatic portion of the aralkyl group defined for R is a heteroaryl group.

A preferred compound of formula Ib is where n is 0 and R is selected from the group consisting of substituted or unsubstituted indole, pyrrole, 7-azaindole, pyrazole, imidazole and indazole.

A preferred compound of formula Ib is where n is 1 and R is selected from the group consisting of substituted or unsubstituted indole, pyrazolyl, phenyl, triazolyl, pyridyl and indazolyl.

A preferred compound of any of the foregoing compounds is where Q is CH_2; Y is O or S; and R is selected from the group consisting of substituted or unsubstituted pyrrole, pyrazole, imidazole, oxazole, isoxazole, thiazole, isothiazole, triazole, tetrazole, indole, 7-azaindole, indazole, purine, pyrrolo-pyrimidine, pyrazolo-pyrimidine, imidazo-pyridine, imidazo-pyrimidine, imidazo-pyridine, pyrrolo-pyridine, pyrrolo- pyridine, pyrrolo-quinoline, pyrrolo-pyrazine, 6,7,8,9-tetrahydropyrido-indole and tetrahydrofuran.

A preferred compound of any of the foegoing compounds is wherein R is selected from the group consisting of substituted or unsubstituted pyrrole, pyrazole, imidazole, oxazole, isoxazole, thiazole, isothiazole, triazole, tetrazole, indole, 7-azaindole, indazole, purine, pyrrolo[2,3-d]pyrimidine, pyrazolo[3,4-d]pyrimidine, imidazo[4,5-b]pyridine, imidazo[1,2-a]pyrimidine, imidazo[1,2-a]pyridine, pyrrolo[3,2-b]pyridine, pyrrolo[3,2-c]pyridine, pyrrolo[2,3-c] pyridine, pyrrolo[3,2-b]quinoline, pyrrolo[2,3-b]pyrazine, 6,7,8,9-tetrahydropyrido[1,2-a]indole, and tetrahydrofuran.

A preferred compound of any of the foregoing compounds is where R is optionally substituted with one or more moieties selected from the group consisting of halogens, trihalomethyl, cyano, hydroxy, nitro, $-NR^5R^6$, carbamoyl, carboxy, carboxamidoxime, $-SO_2NR^5R^6$, $-NHSO_2R^5$, R^7-O-R^8-, R^7-O-R^8-O-R^9-, R^{11}-, R^{11}O-, R^{11}OC(O)-, $R^{11}N(R^5)C(O)$-, $R^{11}C(O)$-, $R^{11}C(O)O$-, $R^{11}S$-, $R^{11}S(O)$-, $R^{11}S(O)_2$-, $(R^5R^6)NC(O)$-, $R^{11}(R^5)NC(O)N(R^5)$-, $R^{11}C(O)N(R^5)$-, $R^{12}(CH_2)_m$-, $R^{12}(CH_2)_mC(O)N(R^5)$-, $R^{12}(CH_2)_mO$-, $R^{12}(CH_2)_mN(R^5)$-, $[R^{12}(CH_2)_m]_2CH$-O-$(CH_2)_m$-, $R^{12}(CH_2)_mOC(O)$-, $R^{12}(CH_2)_mN(R^5)C(O)$-, $R^{12}(CH_2)_mCH(R^{12})(CH_2)_m$-, $R^{12}(CH_2)_mC(O)O$-, $R^{12}(CH_2)_mN(R^5)C(O)O$-, $R^{12}(CH_2)_mOC(O)N(R^5)$-, $R^{12}(CH_2)_mOC(O)O$-, $R^{12}(CH_2)_mN(R^5)C(O)(CH_2)_m$-, $R^{12}(CH_2)_mOC(O)(CH_2)_m$-, $R^{12}(CH_2)_m(CR^5R^6)_m(CH_2)_mN(R^5)(CH_2)_m$-, $R^{12}(CH_2)_mC(O)$-, $R^{12}C(O)(CH_2)_m$-, $R^{12}(CH_2)_m(CR^5R^6)_m(CH_2)_mN(R^5)C(O)(CH_2)_m$-, $R^{12}(CH_2)_m(CR^5R^6)_m(CH_2)_mN(R^5)(CH_2)_mC(O)$-, $[R^{12}(CH_2)_m]_2NC(O)(CH_2)_m$-,

$R^{12}(CH_2)_mC(O)$-, $R^{12}(CH_2)_m(CR^5R^6)_m(CH_2)_mN(R^5)SO_2$-,
$R^{12}(CH_2)_m(CR^5R^6)_m(CH_2)_mO(CH_2)_m$-,

wherein:

R^5 and R^6 for each occurrence are each independently selected from the group consisting of hydrogen, a lower alkyl, benzyl, heteroarylmethyl and aryl group optionally substituted with a halogen, cyano or hydroxy group;

R^7 for each occurrence is independently selected from the group consisting of hydrogen, $R^{10}C(O)$-, a lower alkyl and an aryl group optionally substituted with one or more halogens, cyano, hydroxy or -NR^5R^6;

R^8 and R^9 for each occurrence are each independently selected from the group consisting of -C(O)-, a lower alkyl or an aryl group optionally substituted with one or more halogens, cyano, hydroxy or -NR^5R^6;

R^{10} for each occurrence is independently selected from a group consisting of a lower alkyl and an aryl group optionally substituted with one or more halogens, cyano, hydroxy or -NR^5R^6;

R^{11} for each occurrence is independently hydrogen or selected from an optionally substituted group consisting of a lower alkyl group, a saturated or unsaturated heterocyclic ring, an aryl group and an aralkyl group, where said groups are optionally substituted with one or more halogens, cyano, hydroxy or -NR^5R^6;

R^{12} for each occurrence is independently selected from the group consisting of halogen, carboxy, carbamoyl, lower alkyloxycarbonyl, lower alkenyl, hydroxy, a lower alkyloxy, a lower alcanoyloxy, and -NR^5R^6; or is selected from an optionally substituted group consisting of morpholine, piperazine, piperidine, pyrrolidine, homopiperazine, pyridine, triazole, tetrazole, imidazole and tetrahydropyrane, where said groups are optionally substituted with one or more hydroxy, lower alkyl, lower alkyloxy, lower hydroxyalkyl, lower aminoalkyl, lower alkyloxyalkyl, a saturated or unsaturated heterocyclic ring, cycloalkyl or -NR^5R^6 group; and

m for each occurrence is independently an integer from 0 to 4.

A preferred compound of any of the foregoing compounds is where X is O and n is 0.

A preferred compound of any of the foregoing compounds is where X is S.

A preferred compound of any of the foregoing compounds is where X is NOR_3.

In a particularly preferred embodiment, a preferred compound of any of the foregoing compounds is where R (or R^{13} or R^{17}) is selected from the following substituents:

List I

pyrrol-2-yl
5-methylpyrrol-2-yl
3,5-dimethylpyrrol-2-yl
4,5-dimethylpyrrol-2-yl
4-ethyl-3,5-dimethylpyrrol-2-yl
4-ethoxycarbonyl-3,5-dimethylpyrrol-2-yl
1-methylpyrrol-2-yl
1-(4-hydroxybutyl)pyrrol-2-yl
1-(2-hydroxyethyl)pyrrol-2-yl
1-(3-dimethylaminopropyl)pyrrol-2-yl
4-bromopyrrol-2-yl
1-[N-(2-morpholinoethyl)carbamoylmethyl]pyrrol-2-yl
1-(ethoxycarbonylmethyl)pyrrol-2-yl
1-(carboxymethyl)pyrrol-2-yl
1-[N-(3-dimethylaminopropyl)carbamoylmethyl]pyrrol-2-yl
1-[(4-methylpiperazin-1-yl)carbonylmethyl]pyrrol-2-yl
indol-3-yl
1-(4-hydroxybutyl)indol-3-yl
5-methoxyindol-3-yl
1-(2-hydroxyethyloxymethyl)indol-3-yl
1-(3-dimethylaminopropyl)indol-3-yl
6-methoxycarbonylindol-3-yl
2-methylindol-3-yl
1-methylindol-3-yl
1-isopropylindol-3-yl
1-(2-hydroxy-3-dimethylaminopropyl)indol-3-yl
5-hydroxyindol-3-yl
6-carboxyindol-3-yl
5-amino-2-methylindol-3-yl
6-(2-dimethylaminoethyloxycarbonyl)indol-3-yl

6-(2-morpholinoethyloxycarbonyl)indol-3-yl
6-(3-dimethylaminopropylcarbamoyl)indol-3-yl
1-(carbamoylmethyl)indol-3-yl
8-hydroxymethyl-6,7,8,9-tetrahydropyrido[1,2-a]indol-10-yl
1-(ethoxycarbonylmethyl)indol-3-yl
4-methoxycarbonylindol-3-yl
1-(2-ethoxycarbonylethyl)indol-3-yl
7-methoxycarbonylindol-3-yl
2-ethoxycarbonylindol-3-yl
1-cyclopentylindol-3-yl
1-(3-tetrahydrofuranyl)indol-3-yl
6-(N,N-dimethylaminosulfonyl)indol-3-yl
5-(acetylaminomethyl)indol-3-yl
1-(diethylcarbamoyl)indol-3-yl
5-hydroxy-1-methylindol-3-yl
6-methoxyindol-3-yl
6-hydroxyindol-3-yl
6-[2-(pyrrolidin-1-yl)ethyloxycarbonyl]indol-3-yl
6-(2-dimethylaminoethyloxycarbonyl)-1-methylindol-3-yl
6-(3-dimethylaminopropyloxycarbonyl)indol-3-yl
6-carboxy-1-(2-hydroxyethyl)indol-3-yl
6-{N-[2-(pyrrolidin-1-yl)ethyl]carbamoyl}indol-3-yl
6-[N-(2-morpholinoethyl) carbamoyl]indol-3-yl
6-[N-(2-dimethylaminoethyl)carbamoyl]indol-3-yl
6-{N-[3-(4-methylpiperazin-1-yl)propyl]carbamoyl}indol-3-yl
6-{N-[2-(piperidin-1-yl)ethyl]carbamoyl}indol-3-yl
6-[N- (2-dimethylaminopropyl)carbamoyl]indol-3-yl
6-{[N-(2-dimethylaminoethyl)-N-methyl]carbamoyl}indol-3-yl
6-[(4-methylpiperazin-1-yl)carbonyl]indol-3-yl
5-[2-(piperidin-1-yl)ethyloxy]indol-3-yl
5-(3-dimethylaminopropyloxy)indol-3-yl
5-(2-morpholinoethyloxy) indol-3-yl
5-(3-dimethylaminopropyloxy)-1-(isopropyloxycarbonyl)indol-3-yl
5-(3-dimethylaminopropyloxy)-1-methylindol-3-yl
5-(2-morpholinoethyloxy)-1-methylindol-3-yl
5-[2-(pyrrolidin-1-yl)ethyloxy]indol-3-yl
5-(2-dimethylaminoethyloxy)indol-3-yl
6-(3-dimethylaminopropyloxy)indol-3-yl
6-(2-morpholinoethyloxy)indol-3-yl
6-[2-(piperidin-1-yl)ethyloxy]indol-3-yl
6-[2-(pyrrolidin-1-yl)ethyloxy]indol-3-yl
6-(2-dimethylaminoethyloxy)indol-3-yl

6-[(2-dimethylamino-2-methyl)propyloxy]indol-3-yl
6-[2-(1-methylpyrrolidin-2-yl)ethyloxy]indol-3-yl
6-[2-(1-methylpiperidin-3-yl)methyloxy]indol-3-yl
7-(dimethylaminomethyl)-6-hydroxyindol-3-yl
7-(dimethylaminomethyl)-6-(2-morpholinoethyloxy)indol-3-yl
2-methyl-5-(N′-ethylureido)indol-3-yl
2-methyl-5-(p-toluensulfonylamino)indol-3-yl
6-[(3-dimethylaminopropyl)aminomethyl]indol-3-yl
6-[(2-methoxyethyl)aminomethyl]indol-3-yl
1-(carboxymethyl)indol-3-yl
1-[N-(2-morpholinoethyl)carbamoylmethyl]indol-3-yl
1-[N-(2-methoxyethyl)carbamoylmethyl]indol-3-yl
1-[N-(3-dimethylaminopropyl)carbamoylmethyl]indol-3-yl
1-{N-(2-(2-pyridyl)ethyl) carbamoylmethyl]indol-3-yl
1-{N-[2-(pyrrolidin-1-yl)ethyl]carbamoylmethyl}indol-3-yl
7-[N-(3-dimethylaminopropyl)carbamoyl]indol-3-yl
1-[(4-methylpiperazin-1-yl)carbonylmethyl]indol-3-yl
1-[N,N-bis(2-N′,N′-diethylaminoethyl)carbamoylmethyl]indol-3-yl
1-[(4-piperidinopiperidin-1-yl)carbonylmethyl]indol-3-yl
1-{[N-(2-N′,N′-diethylaminoethyl)-N-methyl]carbamoylmethyl}indol-3-yl
7-carboxyindol-3-yl
7-[(4-methylpiperazin-1-yl)carbonyl]indol-3-yl
7-{[4-(2-hydroxyethyl)piperazin-1-yl]carbonyl}indol-3-yl
7-azaindol-3-yl
1-(4-hydroxybutyl)-7-azaindol-3-yl
1-(2-hydroxyethyloxymethyl)-7-azaindol-3-yl
1-(3-dimethylaminopropyl)-7-azaindol-3-yl
1-(2-morpholinoethyl)-7-azaindol-3-yl
1-(4-acetoxybutyl)-7-azaindol-3-yl
1-(2-hydroxyethyl)-7-azaindol-3-yl
1-methyl-7-azaindol-3-yl
1-methoxymethyl-7-azaindol-3-yl
1-(2-dimethylaminomethyl)-7-azaindol-3-yl
1-(ethoxycarbonylmethyl)-7-azaindol-3-yl
1-[N-(2-morpholinoethyl)carbamoylmethyl] -7-azaindol-3-yl
1-carboxymethyl-7-azaindol-3-yl
1-{N-[3-(4-methylpiperazin-1-yl)propyl]carbamoylmethyl}-7-azaindol-3-yl
1-[(4-methylpiperazin-1-yl)carbamoylmethyl]-7-azaindol-3-yl
1-{[N-(2-N′,N′-diethylaminoethyl)-N-methyl]carbamoylmethyl}-7-azaindol-3-yl
1-{[N-(1-ethylpyrrolidin-2-yl)methyl]carbamoylmethyl}-7-azaindol-3-yl
1-[(4-methylhomopiperazin-1-yl)carbonylmethyl]-7-azaindol-3-yl
1-[(4-ethylpiperazin-1-yl)carbonylmethyl]-7-azaindol-3-yl

1-[(4-piperidinopiperidin-1-yl)carbonylmethyl]-7-azaindol-3-yl
1-[N,N-bis(2-N′,N′-diethylaminoethyl)carbamoylmethyl]-7-azaindol-3-yl
7-benzyloxy pyrrolo[2,3-c]pyridin-5-yl
7-hydroxy pyrrolo[2,3-c]pyridin-5-yl
1-(2-dimethylaminoethyl)-7-hydroxy pyrrolo[2,3-c]pyridin-5-yl
imidazol-2-yl
4-trifluoromethylimidazol-2-yl
4-cyanoimidazol-2-yl
1-methyl-1H-benzo[d]imidazol-2-yl
imidazol-5-yl
4(5)-methylimidazol-5(4)-yl
2-methylimidazol-5-yl
2-ethyl-4(5)-methylimidazol-5(4)-yl
3-(2-diethylaminoethyl)-4-methylimidazol-5-yl
1-(2-diethylaminoethyl)-4-methylimidazol-5-yl
1-(2-morpholinoethyl)-4-methylimidazol-5-yl
3-(2-morpholinoethyl)-4-methylimidazol-5-yl
1-methyl-2-methylthioimidazol-5-yl
4(5)-methoxycarbonylimidazol-5(4)-yl
4(5)-hydroxymethylimidazol-5(4)-yl
furan-3-yl
3-methylpyrazol-4-yl
3-phenylpyrazol-4-yl
1-(2-diethylaminoethyl)-3-methylpyrazol-4-yl
1-(2-diethylaminoethyl)-5-methylpyrazol-4-yl
1-(2-morpholinoethyl)-3-methylpyrazol-4-yl
1-(2-morpholinoethyl)-5-methylpyrazol-4-yl
1-methylpyrazol-4-yl
1-tert-butylpyrazol-4-yl
1-ethoxycarbonylmethyl-3-methylpyrazol-4-yl
1-ethoxycarbonylmethyl-5-methylpyrazol-4-yl
1-carboxymethyl-3-methylpyrazol-4-yl
1-carboxymethyl-5-methylpyrazol-4-yl
1-[N-(2-dimethylaminoethyl)carbamoylmethyl]-3-methylpyrazol-4-yl
1-{N-[3-(4-methylpiperazin-1-yl)propyl]carbamoylmethyl}-3-methylpyrazol-4-yl
1-[N-(2-dimethylaminoethyl)carbamoylmethyl]-5-methylpyrazol-4-yl
1-[N-(2-morpholinoethyl)carbamoylmethyl]-3-methylpyrazol-4-yl
1-[(4-piperidinopiperidin-1-yl)carbonylmethyl]-3-methylpyrazol-4-yl
1-{[N-(2-N′,N′-diethylaminoethyl)-N-methyl]carbamoylmethyl}-3-methylpyrazol-4-yl
1-[(4-methylpiperazin-1-yl)carbonylmethyl]-5-methylpyrazol-4-yl
1-[(4-methylpiperazin-1-yl)carbonylmethyl]-3-methylpyrazol-4-yl
1-{N-[3-(imidazol-1-yl)propyl]carbamoylmethyl}-3-methylpyrazol-4-yl

1-{[4-(2-hydroxyethyl)piperazin-1-yl]carbonylmethyl}-5-methylpyrazol-4-yl
1-{[4-(2-(2-hydroxyethoxy)ethyl)piperazin-1-yl]carbonylmethyl}-5-methylpyrazol-4-yl
indol-2-yl
pyrrol-3-yl
indazol-3-yl
thiazol-2-yl
pyrazol-3-yl
5(3)-ethoxycarbonylpyrazol-3(5)-yl
5(3)-[N-(2-morpholinoethyl)carbamoyl]pyrazol-3(5)-yl
5(3)-[N-(2-methoxyethyl)carbamoyl]pyrazol-3(5)-yl
5(3)-{N-[2-(pyrrolidin-1-yl)ethyl]carbamoyl}pyrazol-3(5)-yl
5(3)-[N-(3-dimethylaminopropyl)carbamoyl] pyrazol-3(5)-yl
2-(dimethylamino)thiazol-5-yl
indol-4-yl
3-(morpholinomethyl)indol-4-yl
indol-7-yl
3-(dimethylaminomethyl)indol-7-yl
3-(morpholinomethyl)indol-7-yl
3-(piperidinomethyl)indol-7-yl
3-[(4-methylpiperazin-1-yl)methyl]indol-7-yl
3,5-dimethyl-4-dimethylaminomethylpyrrol-2-yl
4-carboxyimidazol-2-yl
7-{N-[3-(imidazol-1-yl)propyl]carbamoyl}indol-3-yl
7-{N-[3-(4-methylpiperazin-1-yl)propyl]carbamoyl}indol-3-yl
7-[N- (2-dimethylaminopropyl)carbamoyl]indol-3-yl
7-{N-[2-(pyrrolidin-1-yl)ethyl]carbamoyl}indol-3-yl
7-[(4-ethylpiperazin-1-yl)carbonyl]indol-3-yl
7-[(4-methylhomopiperazin-1-yl)carbonyl]indol-3-yl
3-{[4-(2-hydroxyethyl)piperazin-1-yl]methyl}indol-7-yl
3-[(4-hydroxypiperidin-1-yl)methyl]indol-7-yl
1-[(piperazin-1-yl)carbonylmethyl]-7-azaindol-3-yl
1-[(piperazin-1-yl)carbonylmethyl]indol-3-yl
1-[(piperazin-1-yl)carbonylmethyl]-3-methyl-1H-pyrazol-4-yl
1-{N-[2-(pyrrolidin-1-yl)ethyl]carbamoylmethyl]-3-methyl-1H-pyrazol-4-yl
1-[N-(2-dimethylaminopropyl)carbamoylmethyl]-3-methyl-1H-pyrazol-4-yl
3-(2-dimethylaminoacetyl)indol-7-yl
6-[(2-morpholinoethyl)aminomethyl]indol-3-yl
6-{[2-(pyrrolidin-1-yl)ethyl]aminomethyl]}indol-3-yl
6-[(3-methoxycarbonylpropyl)oxy]indol-3-yl
6-{[(3-(4-methylpiperazin-1-yl)carbonyl]propyloxy}indol-3-yl
6-{3-[N-(2-dimethylaminoethyl)-N-methylcarbamoyl]propyloxy}indol-3-yl
6-[(2-hydroxyethyl)oxymethyloxy]indol-3-yl

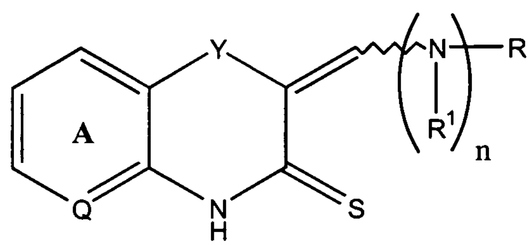
6-{3-[(4-piperidinopiperidin-1-yl)carbonyl]propyloxy}indol-3-yl
6-{3-{[4-(2-hydroxyethyl)piperazin-1-yl]carbonyl}propyloxy}indol-3-yl
6-[(4-methylpiperazin-1-yl)methyl]indol-3-yl
6-{[N-(2-dimethylaminoethyl)-N-methyl]aminomethyl}indol-3-yl
7-(dimethylaminomethyl)-6-(2-methoxyethyloxy)indol-3-yl
7-(dimethylaminomethyl)-6-(3-methoxycarbonylpropyloxy)indol-3-yl
7-(dimethylaminomethyl)-6-{[3-(4-methylpiperazin-1-yl)carbonyl]propyloxy}indol-3-yl
7-(dimethylaminomethyl)-6-[(2-hydroxyethyl)oxymethyloxy]indol-3-yl
6-(2-methoxyethyloxy)-7-[(pyrrolidin-1-yl) methyl]indol-3-yl
6-{[3-(4-methylpiperazin-1-yl)carbonyl]propyloxy}-7-[(pyrrolidin-1-yl) methyl]indol-3-yl
6-[(2-hydroxyethyl)oxymethyloxy]-7-[(pyrrolidin-1-yl)methyl]indol-3-yl
7-[[(pyrrolidin-1-yl)methyl]-6-{[2-(pyrrolidin-1-yl)ethyl]oxy}indol-3-yl
6-[2-(pyrrolidin-1-yl)ethyloxy]-7-azaindol-3-yl
6-(2-piperidinoethyloxy)-7-azaindol-3-yl
6-[(2-dimethylamino-2-methyl)propyloxy]-7-azaindol-3-yl
6[(2-hydroxyethyl)aminomethylcarbonyl]indol-3-yl
6-{[2-(pyrrolidin-1-yl)ethyl]aminomethylcarbonyl}indol-3-yl
6-[(2-diethylaminoethyl)aminomethylcarbonyl]indol-3-yl
4-carbamoylimidazol-2-yl
4(5)-methyl-2-(methylmercapto)imidazol-5(4)-yl
4(5)-methyl-2-(methylsulfonyl)imidazol-5(4)-yl
2-amino-4(5)-methylimidazol-5(4)-yl
4(5)-dimethylaminomethylimidazol-5(4)-yl
4(5)-methylaminomethylimidazol-5(4)-yl
4(5)-diethylaminomethylimidazol-5(4)-yl
6-(N-methylaminosulfonyl)indol-3-yl
6-[N-(3-dimethylaminopropyl)sulfonyl]indol-3-yl
6-{N-[2-(pyrrolidin-1-yl)ethyl]aminosulfonyl}indol-3-yl
6-{N-[2-piperidinoethyl]aminosulfonyl}indol-3-yl
6-[N-(2-morpholinoethyl]aminosulfonyl}indol-3-yl
6-{N-[2-(piperidinomethyl]aminosulfonyl}indol-3-yl
6-{N-[3-(4-methylpiperazin-1-yl)propyl]aminosulfonyl}indol-3-yl
7-[N-(2-morpholinoethyl)carbamoyl]indol-3-yl
7-[N-(2-piperidinoethyl)carbamoyl]indol-3-yl
7-{[N-(2-N',N'-diethylaminoethyl)-N-methyl]carbamoyl} indol-3-yl
7-[N-(2-methoxyethyl)carbamoyl]indol-3-yl
7-[(4-piperidinopiperidin-1-yl)carbonyl]indol-3-yl
7-[(piperazin-1-yl)carbonyl]indol-3-yl
7-{N-[(2,2,N',N'-tetramethyl)propyl]carbamoyl}indol-3-yl
7-{N-[(1-ethylpyrrolidin-2-yl)methyl]carbamoyl}indol-3-yl
7-{N-[2-(2-pyridyl)ethyl]carbamoyl}indol-3-yl

6-{N-[2-(2-pyridyl)ethyl]carbamoyl}indol-3-yl
6-[(4-piperidinopiperidin-1-yl)carbonyl]indol-3-yl
6-[(piperazin-1-yl)carbonyl]indol-3-yl
6-{N-[(2,2,N',N'-tetramethyl)propyl]carbamoyl}indol-3-yl
6-{N-[(1-ethylpyrrolidin-2-yl)methyl]carbamoyl}indol-3-yl
6-[(4-methylhomopiperazin-1-yl)carbonyl]indol-3-yl
6-[(4-butylpiperazin-1-yl)carbonyl]indol-3-yl
6-[(4-ethylpiperazin-1-yl)carbonyl]indol-3-yl
6-{[4-(2-(pyrrolidin-1-yl)ethyl)piperidin-1-yl]carbonyl}indol-3-yl
6-{[N-(3-dimethylamino)prop-2-yl]carbamoyl}indol-3-yl
6-{N-[3-(imidazol-1-yl)propyl]carbamoyl}indol-3-yl
6-{[4-(2-hydroxyethyl)piperazin-1-yl]carbonyl}indol-3-yl
3-[(4-ethylpiperazin-1-yl)methyl]indol-7-yl
3-[(pyrrolidin-1-yl)methyl]indol-7-yl
3-[(4-methylhomopiperazin-1-yl)methyl]indol-7-yl
3-(diethylaminomethyl)indol-7-yl
3-{[N-(2-N'N'-dimethylaminoethyl)-N-methyl]aminomethyl}indol-7-yl
3-[(4-piperidinopiperidin-1-yl)methyl]indol-7-yl
3-(2-piperidinoacetyl)indol-7-yl
3-[2-(pyrrolidin-1-yl)acetyl]indol-7-yl
3-(2-diethylaminoacetyl)indol-7-yl
3-[2-(4-methylpiperazin-1-yl)acetyl]indol-7-yl
3-[2-(4-methylhomopiperazin-1-yl)acetyl]indol-7-yl
3-(2-morpholinoacetyl)indol-7-yl
3-{2-[(2-methoxyethyl)amino]acetyl}indol-7-yl
3-{2-[(2-piperidinoethyl)amino]acetyl}indol-7-yl
3-{2-{[3-(imidazol-1-yl)propyl]amino}acetyl}indol-7-yl
6-[3-(carboxypropyl)oxy]indol-3-yl
6-{3-[(4-methylhomopiperazin-1-yl)carbonyl]propyloxy}indol-3-yl
6-[(2-homopiperidin-1-yl)ethyloxy]indol-3-yl
6-[(2-diethylamino-1-methyl)ethyloxy]indol-3-yl
6-{2-[(tetrahydropyran-2-yl)oxy]ethyloxy}indol-3-yl
6-[(2-hydroxyethyl)oxy]indol-3-yl
6-[2-(isopropyloxyl)ethyloxy]indol-3-yl
6-[2-(methoxyethyl)oxy]indol-3-yl
6-[(3-methoxypropyl)oxy]indol-3-yl
6-[(3-methoxybutyl)oxy]indol-3-yl
6-{[(N,N-diethylcarbamoyl)methyl]oxy}indol-3-yl
7-[2-(piperidin-1-yl)ethyloxy]indol-3-yl
7-[(2-homopiperidin-1-yl)ethyloxy]indol-3-yl
7-[(2-diethylamino-1-methyl)ethyloxy]indol-3-yl
7-{2-[(tetrahydropyran-2-yl)oxy]ethyloxy}indol-3-yl

7-[(2-hydroxyethyl)oxy]indol-3-yl
7-[2-(isopropyloxyl)ethyloxy]indol-3-yl
7-[2-(methoxyethyl)oxy]indol-3-yl
7-[(3-methoxypropyl)oxy]indol-3-yl
7-[(3-methoxybutyl)oxy]indol-3-yl
7-{[(N,N-diethylcarbamoyl)methyl]oxy}indol-3-yl
7-(dimethylaminomethyl)-6-[(2-piperidin-1-yl)ethyloxy]indol-3-yl
7-(dimethylaminomethyl)-6-[(2-homopiperidin-1-yl)ethyloxy]indol-3-yl
7-(dimethylaminomethyl)-6-{2-[(tetrahydropyran-2-yl)oxy]ethyloxy}indol-3-yl
7-(dimethylaminomethyl)-6-[(2-hydroxyethyl)oxy]indol-3-yl
7-(dimethylaminomethyl)-6-[2-(isopropyloxyl)ethyloxy]indol-3-yl
7-(dimethylaminomethyl)-6-[2-(methoxyethyl)oxy]indol-3-yl
7-(dimethylaminomethyl)-6-[(3-methoxypropyl)oxy]indol-3-yl
7-(dimethylaminomethyl)-6-[(3-methoxybutyl)oxy]indol-3-yl
7-[(pyrrolidin-1-yl)methyl)]-6-[(2-piperidin-1-yl)ethyloxy]indol-3-yl
7-[(pyrrolidin-1-yl)methyl)]-6-[(2-homopiperidin-1-yl)ethyloxy]indol-3-yl
7-[(pyrrolidin-1-yl)methyl)]-6-{2-[(tetrahydropyran-2-yl)oxy]ethyloxy}indol-3-yl
7-[(pyrrolidin-1-yl)methyl)]-6-[(2-hydroxyethyl)oxy]indol-3-yl
7-[(pyrrolidin-1-yl)methyl)]-6-[2-(isopropyloxyl)ethyloxy]indol-3-yl
7-[(pyrrolidin-1-yl)methyl)]-6-[2-(methoxyethyl)oxy]indol-3-yl
7-[(pyrrolidin-1-yl)methyl)]-6-[(3-methoxypropyl)oxy]indol-3-yl
7-[(pyrrolidin-1-yl)methyl)]-6-[(3-methoxybutyl)oxy]indol-3-yl
6-[(2-homopiperidin-1-yl)ethyloxy]-7-azaindol-3-yl
6-[(2-diethylamino-1-methyl)ethyloxy]-7-azaindol-3-yl
6-{2-[(tetrahydropyran-2-yl)oxy]ethyloxy}-7-azaindol-3-yl
6-[(2-hydroxyethyl)oxy]-7-azaindol-3-yl
6-[2-(isopropyloxyl)ethyloxy]-7-azaindol-3-yl
6-[2-(methoxyethyl)oxy]-7-azaindol-3-yl
6-[(3-methoxypropyl)oxy]-7-azaindol-3-yl
6-[(3-methoxybutyl)oxy]-7-azaindol-3-yl
6-{[(N,N-diethylcarbamoyl)methyl]oxy}-7-azaindol-3-yl
6-{4-(2-hydroxyethyl)piperazin-1-yl]methyl}indol-3-yl
6-[(4-methylhomopiperazin-1-yl)]methylindol-3-yl
6-[(4-piperidinopiperidin-1-yl)methyl]indol-3-yl
6-{[3-(isopropyloxy)propyl]aminomethyl}indol-3-yl
6-{[3,3-bis(ethyloxy)propyl]aminomethyl}indol-3-yl
6-[(2,2-dimethyl-1,3-dioxolane-4-methane)aminomethyl]indol-3-yl
6-{3-[(2-methoxyethyl)oxypropyl]aminomethyl}indol-3-yl
6-{[3-(ethyloxy)propyl]aminomethyl}indol-3-yl
6-[3-(butyloxy)propyl]aminomethyl]indol-3-yl
6-[(3-methoxypropyl)aminomethyl]indol-3-yl
6- (chloromethylcarbonyl)indol-3-yl

6- [2-(isopropyloxyethyl)aminomethylcarbonyl]indol-3-yl
6-{[(2-piperidin-1-yl)ethyl]aminomethylcarbonyl}indol-3-yl
6-{[(2-homopiperidin-1-yl)ethyl]aminomethylcarbonyl}indol-3-yl
6-{4-(2-hydroxyethyl)piperazin-1-yl]methylcarbonyl}indol-3-yl
6-{[(4-methylhomopiperazin-1-yl)]methyl}carbonylindol-3-yl
6-[(4-piperidinopiperidin-1-yl)methylcarbonyl]indol-3-yl
6-{[3-(isopropyloxy)propyl]aminomethylcarbonyl}indol-3-yl
6-{[3,3-bis(ethyloxy)propyl]aminomethylcarbonyl}indol-3-yl
6-[(2,2-dimethyl-1,3-dioxolane-4-methane)aminomethylcarbonyl]indol-3-yl
6-{3-[(2-methoxyethyl)oxypropyl]aminomethylcarbonyl}indol-3-yl
6-{[3-(ethyloxy)propyl]aminomethylcarbonyl}indol-3-yl
6-[3-(butyloxy)propyl]aminomethylcarbonyl]indol-3-yl
6-[(3-methoxypropyl)aminomethylcarbonyl]indol-3-yl.

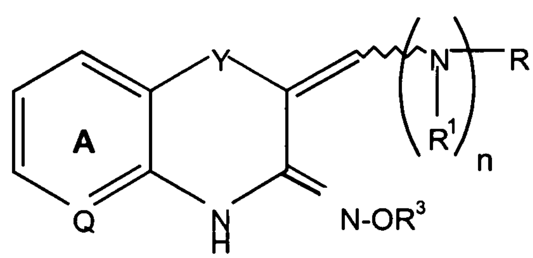
In another embodiment, the compounds of the invention are represented by the formula



V.

and physiologically acceptable salts thereof, wherein ring A is substituted or unsubstituted. Q, Y, R, R^1, and n are defined as above.

In yet another embodiment, the compounds of the invention are represented by the formula



VI.

and physiologically acceptable salts thereof, wherein ring A is substituted or unsubstituted; Q, Y, R, R^1, R^3 and n are defined as above.

In another aspect, the present invention is directed to a method of inhibiting one or more protein kinase activity in a recipient which comprises administering to said recipient any of the foregoing compounds. Preferred is where the compound is a mixture of stereoisomers; even more preferred is where the stereoisomers are enantiomers and most preferred is where the stereoisomers are E and Z isomers. Also preferred is where the compound is a mixture of structural isomers; and more preferred is where the structural isomers are tautomers.

A preferred method of any of the foregoing methods is where said tyrosine kinase is selected from the group consisting of KDR, flt-1, TIE-2, Lck, Src, fyn, Lyn, Blk, and yes.

A preferred method of any of the foregoing methods is where the activity of said tyrosine kinase affects hyperproliferative disorders.

A preferred method of any of the foregoing methods is where the activity of said tyrosine kinase affects angiogenesis.

In another aspect, the present invention provides a pharmaceutical composition comprising any of the compounds described hereinabove or a physiologically acceptable salt thereof and a pharmaceutically acceptable diluent or carrier.

Compounds of formula I may exist as salts with pharmaceutically acceptable acids. The present invention includes such salts. Examples of such salts include hydrochlorides, hydrobromides, sulphates, methanesulphonates, nitrates, maleates, acetates, citrates, fumarates, tartrates [eg (+)-tartrates, (-)-tartrates or mixtures thereof including racemic mixtures], succinates, benzoates and salts with amino acids such as glutamic acid. These salts may be prepared by methods known to those skilled in the art.

Certain compounds of formula I which have acidic substituents may exist as salts with pharmaceutically acceptable bases. The present invention includes such salts. Example of such salts include sodium salts, potassium salts, lysine salts and arginine salts. These salts may be prepared by methods known to those skilled in the art.

Certain compounds of formula I and their salts may exist in more than one

crystal form and the present invention includes each crystal form and mixtures thereof.

Certain compounds of formula I and their salts may also exist in the form of solvates, for example hydrates, and the present invention includes each solvate and mixtures thereof.

Certain compounds of formula I may contain one or more chiral centres, and exist in different optically active forms. When compounds of formula I contain one chiral centre, the compounds exist in two enantiomeric forms and the present invention includes both enantiomers and mixtures of enantiomers. The enantiomers may be resolved by methods known to those skilled in the art, for example by formation of diastereoisomeric salts which may be separated, for example, by crystallization; formation of diastereoisomeric derivatives or complexes which may be separated, for example, by crystallization, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic esterification; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support for example silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step is required to liberate the desired enantiomeric form. Alternatively, specific enantiomers may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into the other by asymmetric transformation.

When a compound of formula I contains more than one chiral centre it may exist in diastereoisomeric forms. The diastereoisomeric pairs may be separated by methods known to those skilled in the art, for example chromatography or crystallization and the individual enantiomers within each pair may be separated as described above. The present invention includes each diastereoisomer of compounds of formula I and mixtures thereof.

Certain compounds of formula I may exist in different tautomeric forms or as different geometric isomers, and the present invention includes each tautomer and/or geometric isomer of compounds of formula I and mixtures thereof.

Certain compounds of formula I may exist in different stable conformational forms which may be separable. Torsional asymmetry due to restricted rotation about an asymmetric single bond, for example because of steric hindrance or ring strain, may permit separation of different conformers. The present invention includes each conformational isomer of compounds of formula I and mixtures thereof.

Certain compounds of formula I may exist in zwitterionic form and the present invention includes each zwitterionic form of compounds of formula I and mixtures thereof.

The compounds of this invention are useful as inhibitors of serine/threonine and tyrosine kinases. In particular, compounds of this invention are useful as inhibitors of tyrosine kinases that are important in hyperproliferative diseases, especially in the process of angiogenesis. Since these compounds are anti-angiogenic, they are important substances for inhibiting the progression disease states where angiogenesis is an important component. Certain compounds of the invention are effective as inhibitors of such serine/threonine kinases as erk, cdks, Plk-1 or Raf-1. These compounds are useful in the treatment of cancer and hyperproliferative disorders.

The present invention provides a method of inhibiting the kinase activity of tyrosine kinases and serine/threonine kinases comprising the administration of a compound represented by formula I to said kinase in sufficient concentration to inhibit the enzyme activity of said kinase.

The present invention further includes the use of these compounds in pharmaceutical compositions with a pharmaceutically effective amount of the above-described compounds and a pharmaceutically acceptable carrier or excipient. These pharmaceutical compositions can be administered to individuals to slow or halt the process of angiogenesis in angiogenesis-aided diseases, or to treat edema, effusions, exudates, or ascites and other conditions associated with vascular hyperpermeability. Certain pharmaceutical compositions can be administered to individuals to treat cancer and hyperproliferative disorders by inhibiting serine/threonine kinases such as cdk, Plk-1, erk, etc.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention have antiangiogenic properties. These antiangiogenic properties are due at least in part to the inhibition of protein tyrosine kinases essential for angiogenic processes. For this reason, these compounds can be used as active agents against such disease states as arthritis, atherosclerosis, psoriasis, hemangiomas, myocardial angiogenesis, coronary and cerebral collaterals, ischemic limb angiogenesis, wound healing, peptic ulcer Helicobacter related diseases, fractures, Crow-Fukase syndrome (POEMS), preeclampsia, menometrorrhagia, cat scratch fever, rubeosis, neovascular glaucoma and retinopathies such as those associated with diabetic retinopathy, retinopathy of prematurity, or age-related macular degeneration. In addition, some of these compounds can be used as active agents against solid tumors, malignant ascites, hematopoietic cancers and hyperproliferative disorders such as thyroid hyperplasia (especially Grave's disease), and cysts (such as hypervascularity of ovarian stroma characteristic of polycystic ovarian syndrome (Stein-Leventhal syndrome)) since such diseases require a proliferation of blood vessel cells for growth and/or metastasis.

Further, some of these compounds can be used as active agents against burns, chronic lung disease, stroke, polyps, anaphylaxis, chronic and allergic inflammation, ovarian hyperstimulation syndrome, brain tumor-associated cerebral edema, high-altitude, trauma or hypoxia induced cerebral or pulmonary edema, ocular and macular edema, ascites, and other diseases where vascular hyperpermeability, effusions, exudates, protein extravasation, or edema is a manifestation of the disease. The compounds will also be useful in treating disorders in which protein extravasation leads to the deposition of fibrin and extracellular matrix, promoting stromal proliferation (e.g. keloid, fibrosis, cirrhosis and carpal tunnel syndrome).

VEGF's are unique in that they are the only angiogenic growth factors known to contribute to vascular hyperpermeability and the formation of edema. Indeed, vascular

hyperpermeability and edema that is associated with the expression or administration of many other growth factors appears to be mediated via VEGF production. Inflammatory cytokines stimulate VEGF production. Hypoxia results in a marked upregulation of VEGF in numerous tissues, hence situations involving infarct, occlusion, ischemia, anemia, or circulatory impairment typically invoke VEGF/VPF mediated responses. Vascular hyperpermeability, associated edema, altered transendothelial exchange and macromolecular extravasation, which is often accompanied by diapedesis, can result in excessive matrix deposition, aberrant stromal proliferation, fibrosis, etc. Hence, VEGF-mediated hyperpermeability can significantly contribute to disorders with these etiologic features.

It is envisaged that the disorders listed above are mediated to a significant extent by protein tyrosine kinase activity involving the KDR/VEGFR-2 and/or the Flt-1/VEGFR-1 tyrosine kinases. By inhibiting the activity of these tyrosine kinases, the progression of the listed disorders is inhibited because the angiogenic or vascular hyperpermeability component of the disease state is severely curtailed. The action of certain compounds of this invention, by their selectivity for specific tyrosine kinases, result in a minimization of side effects that would occur if less selective tyrosine kinase inhibitors were used.

The compounds of this invention have inhibitory activity against protein kinases. That is, these compounds modulate signal transduction by protein kinases. Compounds of this invention inhibit protein kinases from serine/threonine and tyrosine kinase classes. In particular, these compounds selectively inhibit the activity of the KDR/FLK-1/VEGFR-2 tyrosine kinases. Certain compounds of this invention also inhibit the activity of additional tyrosine kinases such as Flt-1/VEGFR-1, Src-subfamily kinases such as Lck, Src, fyn, yes, etc. Additionally, some compounds of this invention significantly inhibit serine/threonine kinases such as CDKs, Plk-1, or Raf-1 which play an essential role in cell-cycle progression. The potency and specificity of the generic compounds of this invention towards a particular protein kinase can often be altered and

optimized by variations in the nature, number and arrangement of the substituents (i.e., R_1, R_2, R_3, R_4, R_5 and R_6) of and conformational restrictions. In addition the metabolites of certain compounds may also possess significant protein kinase inhibitory activity.

The compounds of this invention, when administered to individuals in need of such compounds, inhibit vascular hyperpermeability and the formation of edema in these individuals. These compounds act, it is believed, by inhibiting the activity of KDR tyrosine kinase which is involved in the process of vascular hyperpermeability and edema formation. The KDR tyrosine kinase may also be referred to as FLK-1 tyrosine kinase, NYK tyrosine kinase or VEGFR-2 tyrosine kinase. KDR tyrosine kinase is activated when vascular endothelial cell growth factor (VEGF) or another activating ligand (such as VEGF-C, VEGF-D or HIV Tat protein) binds to a KDR tyrosine kinase receptor which lies on the surface of vascular endothelial cells. Following such KDR tyrosine kinase activation, hyperpermeability of the blood vessels occurs and fluid moves from the blood stream past the blood vessel walls into the interstitial spaces, thereby forming an area of edema. Diapedesis also often accompanies this response. Similarly, excessive vascular hyperpermeability can disrupt normal molecular exchange across the endothelium in critical tissues and organs (e.g., lung and kidney), thereby causing macromolecular extravasation and deposition. Following this acute response to KDR stimulation which is believed to facilitate the subsequent angiogenic process, prolonged KDR tyrosine kinase stimulation results in the proliferation and chemotaxis of vascular endothelial cells and formation of new vessels. By inhibiting KDR tyrosine kinase activity, either by blocking the production of the activating ligand, by blocking the activating ligand binding to the KDR tyrosine kinase receptor, by preventing receptor dimerization and transphosphorylation, by inhibiting the enzyme activity of the KDR tyrosine kinase (inhibiting the phosphorylation function of the enzyme) or by some other mechanism that interrupts its downstream signaling (D. Mukhopedhyay *et al.*, *Cancer Res. 58:*1278-1284 (1998) and references therein), hyperpermeability, as well as

associated extravasation, subsequent edema formation and matrix deposition, and angiogenic responses, may be inhibited and minimized.

One group of preferred compounds of this invention have the property of inhibiting KDR tyrosine kinase activity without significantly inhibiting Flt-1 tyrosine kinase activity (Flt-1 tyrosine kinase is also referred to as VEGFR-1 tyrosine kinase). Both KDR tyrosine kinase and Flt-1 tyrosine kinase are activated by VEGF binding to KDR tyrosine kinase receptors and to Flt-1 tyrosine kinase receptors, respectively. Since Flt-1 tyrosine kinase activity may mediate important events in endothelial maintenance and vascular function, an inhibition of this enzyme activity may lead to toxic or adverse effects. At the very least, such inhibition is unnecessary for blocking the angiogenic responses, induction of vascular hyperpermeability and the formation of edema, so it is wasteful and of no value to the individual. Certain preferred compounds of this invention are unique because they inhibit the activity of one VEGF-receptor tyrosine kinase (KDR) that is activated by activating ligands but do not inhibit other receptor tyrosine kinases, such as Flt-1, that are also activated by certain activating ligands. The preferred compounds of this invention are, therefore, selective in their tyrosine kinase inhibitory activity.

The compounds of the present invention are also useful in the treatment of ulcers - bacterial, fungal, Mooren ulcers and ulcerative colitis.

The compounds of the present invention are also useful in the treatment of conditions wherein undesired angiogenesis, edema, or stromal deposition occurs in viral infections such as Herpes simplex, Herpes Zoster, AIDS, psoriasis, Kaposi's sarcoma, protozoan infections and toxoplasmosis, endometriosis, ovarian hyperstimulation syndrome, preeclampsia, menometrorrhagia, systemic lupus, sarcoidosis, synovitis, Crohn's disease, sickle cell anaemia, Lyme's disease, pemphigoid, Paget's disease, hyperviscosity syndrome, Osler-Weber-Rendu disease, chronic inflammation, chronic occlusive pulmonary disease, asthma, rheumatoid arthritis and osteoarthritis, and edema following trauma, radiation, or stroke.

The compounds of the present invention are also useful in the treatment of ocular conditions such as ocular and macular edema, ocular neovascular disease, scleritis, radial keratotomy, uveitis, vitritis, myopia, optic pits, chronic retinal detachment, post-laser complications, conjunctivitis, Stargardt's disease and Eales disease in addition to retinopathy and macular degeneration.

The compounds of the present invention are also useful in the treatment of cardiovascular conditions such as atherosclerosis, restenosis, vascular occlusion and carotid obstructive disease.

The compounds of the present invention are also useful in the treatment of cancer related indications such as solid tumors, sarcomas (especially Ewing's sarcoma and osteosarcoma), retinoblastoma, rhabdomyosarcomas, neuroblastoma, hematopoietic malignancies, including leukaemia and lymphoma, tumor-induced pleural or pericardial effusions, and malignant ascites.

The compounds of the present invention are also useful in the treatment of Crow-Fukase (POEMS) syndrome and diabetic conditions such as glaucoma, diabetic retinopathy and microangiopathy.

It is envisaged that the disorders listed above are mediated to a significant extent by protein tyrosine kinase activity involving the VEGF receptors (e.g. KDR and Flt-1). By inhibiting the activity of these receptor tyrosine kinases, the progression of the listed disorders is inhibited because the angiogenic component of the disease state is severely curtailed. The action of the compounds of this invention, by their selectivity for specific tyrosine kinases, result in a minimization of side effects that would occur if less selective tyrosine kinase inhibitors were used.

In another aspect the present invention provides compounds of formula I as defined initially above (including the provisos) for use as medicaments, particularly as inhibitors of protein kinase activity for example tyrosine kinase activity, serine kinase activity and threonine kinase activity. In yet another aspect the present invention provides the use of compounds of formula I as defined initially above (including the

provisos) in the manufacture of a medicament for use in the inhibition of protein kinase activity.

In this invention, the following definitions are applicable:

" Physiologically acceptable salts" refers to those salts which retain the biological effectiveness and properties of the free bases and which are obtained by reaction with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid or organic acids such as sulfonic acid, carboxylic acid, organic phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, lactic acid, tartaric acid and the like.

Pharmaceutical Formulations

The compounds of this invention can be administered to a human patient by themselves or in pharmaceutical compositions where they are mixed with suitable carriers or excipient(s) at doses to treat or ameliorate vascular hyperpermeability, edema and associated disorders. Mixtures of these compounds can also be administered to the patient as a simple mixture or in suitable formulated pharmaceutical compositions. A therapeutically effective dose further refers to that amount of the compound or compounds sufficient to result in the prevention or attenuation of inappropriate neovascularization, progression of hyperproliferative disorders, edema, VEGF-associated hyperpermeability and/or VEGF-related hypotension. Techniques for formulation and administration of the compounds of the instant application may be found in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA, latest edition.

Routes of Administration

Suitable routes of administration may, for example, include oral, eyedrop, rectal, transmucosal, topical, or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections.

Alternatively, one may administer the compound in a local rather than a systemic manner, for example, via injection of the compound directly into an edematous site, often in a depot or sustained release formulation.

Furthermore, one may administer the drug in a targeted drug delivery system, for example, in a liposome coated with endothelial cell-specific antibody.

Composition/Formulation

The pharmaceutical compositions of the present invention may be manufactured in a manner that is itself known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

Pharmaceutical compositions for use in accordance with the present invention thus may be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

For injection, the agents of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by combining the active compound with a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in

particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of pressurized aerosol the dosage unit may be

determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds may be formulated for parenteral administration by injection, e.g. bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly or by intramuscular injection). Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or

ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

An example of a pharmaceutical carrier for the hydrophobic compounds of the invention is a cosolvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. The cosolvent system may be the VPD co-solvent system. VPD is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant polysorbate 80, and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. The VPD co-solvent system (VPD:5W) consists of VPD diluted 1:1 with a 5% dextrose in water solution. This co-solvent system dissolves hydrophobic compounds well, and itself produces low toxicity upon systemic administration. Naturally, the proportions of a co-solvent system may be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of polysorbate 80; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, e.g. polyvinyl pyrrolidone; and other sugars or polysaccharides may substitute for dextrose.

Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as dimethysulfoxide also may be employed, although usually at the cost of greater toxicity. Additionally, the compounds may be delivered topically and by using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for stabilization may be employed.

The pharmaceutical compositions also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include but are not limited to calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

Many of the organic molecule compounds of the invention may be provided as salts with pharmaceutically compatible counterions. Pharmaceutically compatible salts may be formed with many acids, including but not limited to hydrochloric, sulfuric, maleic, acetic, lactic, tartaric, malic, succinic, etc. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free base forms.

Effective Dosage

Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an effective amount to achieve its intended purpose. More specifically, a therapeutically effective amount means an amount effective to prevent development of or to alleviate the existing symptoms of the subject being treated. Determination of the effective amounts is well within the capability of those skilled in the art.

For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from cellular assays. For example, a dose can be formulated in cellular and animal models to achieve a circulating concentration range that includes the IC_{50} as determined in cellular assays (i.e., the concentration of the test compound which achieves a half-maximal inhibition of a given protein kinase activity). In some cases it is appropriate to determine the *in vitro* or cellular IC_{50} in the presence of 3 to 5% serum albumin since such a determination approximates the binding effects of plasma protein on the compound. Such information can be used to more accurately determine useful doses in humans. Further, the most preferred compounds for systemic administration effectively inhibit protein kinase signaling in intact cells at levels that are safely achievable in plasma.

A therapeutically effective dose refers to that amount of the compound that results in amelioration of symptoms in a patient. Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the maximum tolerated dose (MTD) and the ED_{50} (effective dose for 50% maximal response). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between MTD and ED_{50}. Compounds which exhibit high therapeutic indices are preferred. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (See e.g. Fingl *et al.*, 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p1). In the treatment of crises, the administration of an acute bolus or an infusion approaching the MTD may be required to obtain a rapid response.

Dosage amount and interval may be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the kinase modulating effects, or minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from *in vitro* data; e.g. the concentration necessary to achieve 50-90% inhibition of protein kinase using the assays described herein. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. However, HPLC assays or bioassays can be used to determine plasma concentrations.

Dosage intervals can also be determined using the MEC value. Compounds should be administered using a regimen which maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-

90% until the desired amelioration of symptoms is achieved. In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration.

The amount of composition administered will, of course, be dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration and the judgment of the prescribing physician.

Packaging

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. Compositions comprising a compound of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

In some formulations it may be beneficial to use the compounds of the present invention in the form of particles of very small size, for example as obtained by fluid energy milling.

The use of compounds of the present invention in the manufacture of pharmaceutical compositions is illustrated by the following description. In this description the term "active compound" denotes any compound of the invention but particularly any compound which is the final product of one of the preceding Examples.

a) <u>Capsules</u>

In the preparation of capsules, 10 parts by weight of active compound and 240 parts by weight of lactose are de-aggregated and blended. The mixture is filled into hard gelatin capsules, each capsule containing a unit dose or part of a unit dose of active compound.

b) Tablets

Tablets are prepared from the following ingredients.

	Parts by weight
Active compound	10
Lactose	190
Maize starch	22
Polyvinylpyrrolidone	10
Magnesium stearate	3

The active compound, the lactose and some of the starch are de-aggregated, blended and the resulting mixture is granulated with a solution of the polyvinyl-pyrrolidone in ethanol. The dry granulate is blended with the magnesium stearate and the rest of the starch. The mixture is then compressed in a tabletting machine to give tablets each containing a unit dose or a part of a unit dose of active compound.

c) Enteric coated tablets

Tablets are prepared by the method described in (b) above. The tablets are enteric coated in a conventional manner using a solution of 20% cellulose acetate phthalate and 3% diethyl phthalate in ethanol:dichloromethane (1:1).

d) Suppositories

In the preparation of suppositories, 100 parts by weight of active compound is incorporated in 1300 parts by weight of triglyceride suppository base and the mixture formed into suppositories each containing a therapeutically effective amount of active ingredient.

In the compositions of the present invention the active compound may, if desired, be associated with other compatible pharmacologically active ingredients. For example, the compounds of this invention can be administered in combination with one or more additional pharmaceutical agents that inhibit or prevent the production of VEGF, attenuate intracellular responses to VEGF, block intracellular signal transduction, inhibit vascular hyperpermeability, reduce inflammation, or inhibit or prevent the formation of

edema or neovascularization. The compounds of the invention can be administered prior to, subsequent to or simultaneously with the additional pharmaceutical agent, whichever course of administration is appropriate. The additional pharmaceutical agents include but are not limited to anti-edemic steroids, NSAIDS, ras inhibitors, anti-TNF agents, anti-IL1 agents, antihistamines, PAF-antagonists, COX-1 inhibitors, COX-2 inhibitors, NO synthase inhibitors, PKC inhibitors and PI3 kinase inhibitors. The compounds of the invention and the additional pharmaceutical agents act either additively or synergistically. Thus, the administration of such a combination of substances that inhibit angiogenesis, vascular hyperpermeability and/or inhibit the formation of edema can provide greater relief from the deletrious effects of a hyperproliferative disorder, angiogenesis, vascular hyperpermeability or edema than the administration of either substance alone. In the treatment of malignant disorders combinations with antiproliferative or cytotoxic chemotherapies or radiation are anticipated.

The present invention also comprises the use of a compound of formula I as a medicament.

Both the Src and Syk families of kinases play pivotal roles in the regulation of immune function. The Src family currently includes Fyn, Lck, Fgr, Fes, Lyn, Src, Yes, Hck, and Blk. The Syk family is currently understood to include only Zap and Syk. The Janus family of kinases is involved in the transduction of growth factor and pro-inflammatory cytokine signals through a number of receptors. Although BTK and ITK, members of the Tec family of kinases, play a less well understood role in immunobiology, their modulation by an inhibitor may prove therapeutically beneficial. The kinases RIP, IRAK-1, IRAK-2, NIK, IKK-1 and IKK-2 are involved in the signal transduction pathways for the key pro-inflammatory cytokines TNF and IL-1. By virtue of their ability to inhibit one or more of these kinases, compounds of formula I may function as immunomodulatory agents useful for the maintenance of allografts and the treatment of autoimmune disorders. Through their ability to regulate T cell activation or the potentiation of an inflammatory process, these compounds could be used to treat

such autoimmune diseases. Transplants due to rejection phenomena, either host versus graft for solid organs or graft versus host for bone marrow, are limited by the toxicity of currently available immunosuppressive agents and would benefit from an efficacious drug with improved therapeutic index. Gene targeting experiments have demonstrated the essential role of Src in the biology of osteoclasts, the cells responsible for bone resorption. Compounds of formula I, through their ability to regulate Src, may also be useful in the treatment of osteoporosis, osteopetrosis, Paget's disease, tumor-induced hypercalcemia and in the treatment of bone metastases.

A number of protein kinases have been demonstrated to be protooncogenes. Chromosome breakage (at the ltk kinase break point on chromosome 5), translocation as in the case of the Abl gene with BCR (Philadelphia chromosome), truncation in instances such as c-Kit or EGFR, or mutation (e.g., Met) result in the creation of dysregulated proteins converting them from protooncogene to oncogene products. In other tumors, oncogenesis is driven by an autocrine or paracrine ligand/growth factor receptor interactions. Members of the src-family kinases are typically involved in downstream signal transduction thereby potentiating the oncogenesis and themselves may become oncogenic by over-expression or mutation. By inhibiting the protein kinase activity of these proteins the disease process may be disrupted. Vascular restenosis may involve process of FGF and/or PDGF - promoted smooth muscle and endothelial cell proliferation. Inhibition of FGFr or PDGFr kinase activity may be an efficacious strategy for inhibiting this phenomenon. Thus compounds of formula I which inhibit the kinase activity of normal or aberrant c-kit, c-met, c-fms, src-family members, EGFr, erbB2, erbB4, BCR-Abl, PDGFr, FGFr, and other receptor or cytosolic tyrosine kinases may be of value in the treatment of benign and neoplastic proliferative diseases.

In many pathological conditions (for example, solid primary tumors and metastases, Kaposi's sarcoma, rheumatoid arthritis, blindness due to inappropriate ocular neovascularization, psoriasis and atherosclerosis) disease progression is contingent upon persistent angiogenesis. Polypeptide growth factors often produced by the disease tissue

or associated inflammatory cells, and their corresponding endothelial cell specific receptor tyrosine kinases (e.g., KDR/VEGFR-2, Flt-1/VEGFR-1, Tie-2/Tek and Tie) are essential for the stimulation of endothelial cell growth, migration, organization, differentiation and the establishment of the requisite new functional vasculature. As a result of the "vascular permeability factor" activity of VEGF in mediating vascular hyperpermeability, VEGF-stimulation of a VEGFR kinase is also believed to play an important role in the formation of tumor ascites, cerebral and pulmonary edema, pleural and pericardial effusions, delayed-type hypersensitivity reactions, tissue edema and organ dysfunction following trauma, burns, ischemia, diabetic complications, endometriosis, adult respiratory distress syndrome (ARDS), post-cardiopulmonary bypass-related hypotension and hyperpermeability, and ocular edema leading to glaucoma or blindness due to inappropriate neovascularization. In addition to VEGF, recently identified VEGF-C and VEGF-D, and HIV-Tat protein can also cause a vascular hyperpermeability response through the stimulation of a VEGFR kinase. Tie-2 is expressed also in a select population of hematopoietic stem cells in which it may play a role in their recruitment, adhesion, regulation and differentiation (*Blood* 89, 4317-4326 (1997)); this Tie-2 expressing population may serve as circulating angiogenic endothelial progenitors. Certain agents according to formula I capable of blocking the kinase activity of endothelial cell specific kinases could therefore inhibit disease progression involving these situations.

The compounds of formula I or a salt thereof or pharmaceutical compositions containing a therapeutically effective amount thereof may be used in the treatment of benign and neoplastic proliferative diseases and disorders of the immune system. Such diseases include autoimmune diseases, such as rheumatoid arthritis, thyroiditis, type 1 diabetes, multiple sclerosis, sarcoidosis, inflammatory bowel disease, myasthenia gravis and systemic lupus erythematosus; psoriasis, organ transplant rejection (eg. kidney rejection, graft versus host disease), benign and neoplastic proliferative diseases, human cancers such as lung, breast, stomach, bladder, colon, pancreas, ovarian, prostate and

rectal cancer and hematopoietic malignancies (leukemia and lymphoma), and diseases involving inappropriate vascularization for example diabetic retinopathy, retinopathy of prematurity, choroidal neovascularization due to age-related macular degeneration, and infantile hemangiomas in human beings. In addition, such inhibitors may be useful in the treatment of disorders involving VEGF mediated edema, ascites, effusions, and exudates, including for example macular edema, cerebral edema, and adult respiratory distress syndrome (ARDS).

The compounds of the present invention may also be useful in the prophylaxis of the above diseases.

A further aspect of the present invention provides the use of a compound of formula I or a salt thereof in the manufacture of a medicament for treating vascular hyperpermeability, angiogenesis-dependent disorders, proliferative diseases and/or disorders of the immune system in mammals, particularly human beings.

The present invention also provides a method of treating vascular hyperpermeability, inappropriate neovascularization, proliferative diseases and/or disorders of the immune system which comprises the administration of a therapeutically effective amount of a compound of formula I to a mammal, particularly a human being, in need thereof.

The *in vitro* potency of compounds in inhibiting these protein kinases may be determined by the procedures detailed below.

The potency of compounds can be determined by the amount of inhibition of the phosphorylation of an exogenous substrate (e.g., synthetic peptide (Z. Songyang *et al.*, *Nature*. 373:536-539) by a test compound relative to control.

KDR Tyrosine Kinase Production Using Baculovirus System:

The coding sequence for the human KDR intra-cellular domain (aa789-1354) was generated through PCR using cDNAs isolated from HUVEC cells. A poly-His6 sequence was introduced at the N-terminus of this protein as well. This fragment was

cloned into transfection vector pVL1393 at the Xba 1 and Not 1 site. Recombinant baculovirus (BV) was generated through co-transfection using the BaculoGold Transfection reagent (PharMingen). Recombinant BV was plaque purified and verified through Western analysis. For protein production, SF-9 cells were grown in SF-900-II medium at 2 x 106/ml, and were infected at 0.5 plaque forming units per cell (MOI). Cells were harvested at 48 hours post infection.

Purification of KDR

SF-9 cells expressing $(His)_6$KDR(aa789-1354) were lysed by adding 50 ml of Triton X-100 lysis buffer (20 mM Tris, pH 8.0, 137 mM NaCl, 10% glycerol, 1% Triton X-100, 1mM PMSF, 10µg/ml aprotinin, 1 µg/ml leupeptin) to the cell pellet from 1L of cell culture. The lysate was centrifuged at 19,000 rpm in a Sorval SS-34 rotor for 30 min at 4°C. The cell lysate was applied to a 5 ml $NiCl_2$ chelating sepharose column, equilibrated with 50 mM HEPES, pH7.5, 0.3 M NaCl. KDR was eluted using the same buffer containing 0.25 M imidazole. Column fractions were analyzed using SDS-PAGE and an ELISA assay (below) which measures kinase activity. The purified KDR was exchanged into 25mM HEPES, pH7.5, 25mM NaCl, 5 mM DTT buffer and stored at -80°C.

Human Tie-2 Kinase Production and Purification

The coding sequence for the human Tie-2 intra-cellular domain (aa775-1124) was generated through PCR using cDNAs isolated from human placenta as a template. A poly-His_6 sequence was introduced at the N-terminus and this construct was cloned into transfection vector pVL 1939 at the Xba 1 and Not 1 site. Recombinant BV was generated through co-transfection using the BaculoGold Transfection reagent (PharMingen). Recombinant BV was plaque purified and verified through Western analysis. For protein production, SF-9 insect cells were grown in SF-900-II medium at 2 x 106/ml, and were infected at MOI of 0.5. Purification of the His-tagged kinase used in screening was analogous to that described for KDR.

Human Flt-1 Tyrosine Kinase Production and Purification

The baculoviral expression vector pVL1393 (Phar Mingen, Los Angeles, CA) was used. A nucleotide sequence encoding poly-His6 was placed 5' to the nucleotide region encoding the entire intracellular kinase domain of human Flt-1 (amino acids 786-1338). The nucleotide sequence encoding the kinase domain was generated through PCR using cDNA libraries isolated from HUVEC cells. The histidine residues enabled affinity purification of the protein as a manner analogous to that for KDR and ZAP70. SF-9 insect cells were infected at a 0.5 multiplicity and harvested 48 hours post infection.

EGFR Tyrosine Kinase Source

EGFR was purchased from Sigma (Cat # E-3641; 500 units/50 µl) and the EGF ligand was acquired from Oncogene Research Products/Calbiochem (Cat # PF011-100).

Expression of ZAP70

The baculoviral expression vector used was pVL1393. (Pharmingen, Los Angeles, Ca.) The nucleotide sequence encoding amino acids M(H)6 LVPR$_9$S was placed 5' to the region encoding the entirety of ZAP70 (amino acids 1-619). The nucleotide sequence encoding the ZAP70 coding region was generated through PCR using cDNA libraries isolated from Jurkat immortalized T-cells. The histidine residues enabled affinity purification of the protein (vide infra). The LVPR$_9$S bridge constitutes a recognition sequence for proteolytic cleavage by thrombin, enabling removal of the affinity tag from the enzyme. SF-9 insect cells were infected at a multiplicity of infection of 0.5 and harvested 48 hours post infection.

Extraction and purification of ZAP70

SF-9 cells were lysed in a buffer consisting of 20 mM Tris, pH 8.0, 137 mM NaCl, 10% glycerol, 1% Triton X-100, 1 mM PMSF, 1 µg/ml leupeptin, 10 µg/ml aprotinin and 1 mM sodium orthovanadate. The soluble lysate was applied to a chelating sepharose HiTrap column (Pharmacia) equilibrated in 50 mM HEPES, pH 7.5,

0.3 M NaCl. Fusion protein was eluted with 250 mM imidazole. The enzyme was stored in buffer containing 50 mM HEPES, pH 7.5, 50 mM NaCl and 5 mM DTT.

Lck source

Lck or truncated forms of Lck may be commercially obtained (e.g. from Upstate Biotechnology Inc. (Saranac Lake, N.Y) and Santa Cruz Biotechnology Inc. (Santa Cruz, Ca.)) or purified from known natural or recombinant sources using conventional methods.

Enzyme Linked Immunosorbent Assay (ELISA) For PTKs

Enzyme linked immunosorbent assays (ELISA) were used to detect and measure the presence of tyrosine kinase activity. The ELISA were conducted according to known protocols which are described in, for example, Voller, *et al.*, 1980, "Enzyme-Linked Immunosorbent Assay," In: *Manual of Clinical Immunology, 2d ed.,* edited by Rose and Friedman, pp 359-371 Am. Soc. of Microbiology, Washington, D.C.

The disclosed protocol was adapted for determining activity with respect to a specific PTK. For example, preferred protocols for conducting the ELISA experiments is provided below. Adaptation of these protocols for determining a compound's activity for other members of the receptor PTK family, as well as non-receptor tyrosine kinases, are well within the abilities of those in the art. For purposes of determining inhibitor selectivity, a universal PTK substrate (e.g., random copolymer of poly(Glu_4 Tyr), 20,000-50,000 MW) was employed together with ATP (typically 5 μM) at concentrations approximately twice the apparent Km in the assay.

The following procedure was used to assay the inhibitory effect of compounds of this invention on KDR, Flt-1, Flt-4/VEGFR-3, Tie-2, EGFR and ZAP70 tyrosine kinase activity:

Buffers and Solutions:

PGT: Poly (Glu,Tyr) 4:1

Store powder at -20°C. Dissolve powder in phosphate buffered saline (PBS) for 50mg/ml solution. Store 1ml aliquots at -20°C. When making plates dilute to 250μg/ml in Gibco PBS.

Reaction Buffer: 100mM Hepes, 20mM $MgCl_2$, 4mM $MnCl_2$, 5mM DTT, 0.02%BSA, 200μM $NaVO_4$, pH 7.10

ATP: Store aliquots of 100mM at -20°C. Dilute to 20μM in water

Washing Buffer: PBS with 0.1% Tween 20

Antibody Diluting Buffer: 0.1% bovine serum albumin (BSA) in PBS

TMB Substrate: mix TMB substrate and Peroxide solutions 9:1 just before use or use K-Blue Substrate from Neogen

Stop Solution: 1M Phosphoric Acid

Procedure

1. Plate Preparation:

Dilute PGT stock (50mg/ml, frozen) in PBS to a 250μg/ml. Add 125μl per well of Corning modified flat bottom high affinity ELISA plates (Corning #25805-96). Add 125μl PBS to blank wells. Cover with sealing tape and incubate overnight 37°C. Wash 1x with 250μl washing buffer and dry for about 2hrs in 37°C dry incubator.

Store coated plates in sealed bag at 4°C until used.

2. Tyrosine Kinase Reaction:

-Prepare inhibitor solutions at a 4x concentration in 20% DMSO in water.

-Prepare reaction buffer

-Prepare enzyme solution so that desired units are in 50μl, e.g. for KDR make to 1 ng/μl for a total of 50ng per well in the reactions. Store on ice.

-Make 4x ATP solution to 20μM from 100mM stock in water. Store on ice

-Add 50μl of the enzyme solution per well (typically 5-50 ng enzyme/well depending on the specific activity of the kinase)

-Add 25µl 4x inhibitor

-Add 25µl 4x ATP for inhibitor assay

-Incubate for 10 minutes at room temperature

-Stop reaction by adding 50µl 0.05N HCl per well

-Wash plate

**Final Concentrations for Reaction: 5µM ATP, 5% DMSO

3. Antibody Binding

-Dilute 1mg/ml aliquot of PY20-HRP (Pierce) antibody (a phosphotyrosine antibody) to 50ng/ml in 0.1% BSA in PBS by a 2 step dilution (100x, then 200x)

-Add 100µl Ab per well. Incubate 1 hr at room temp. Incubate 1hr at 4C.

-Wash 4x plate

4. Color reaction

-Prepare TMB substrate and add 100µl per well

-Monitor OD at 650nm until 0.6 is reached

-Stop with 1M Phosphoric acid. Shake on plate reader.

-Read OD immediately at 450nm

Optimal incubation times and enzyme reaction conditions vary slightly with enzyme preparations and are determined empirically for each lot.

For Lck, the Reaction Buffer utilized was 100 mM MOPSO, pH 6.5, 4 mM $MnCl_2$, 20 mM $MgCl_2$, 5 mM DTT, 0.2% BSA, 200 mM $NaVO_4$ under the analogous assay conditions.

Compounds of formula I may have therapeutic utility in the treatment of diseases involving both identified, including those not mentioned herein, and as yet unidentified protein tyrosine kinases which are inhibited by compounds of formula I. All compounds exemplified herein significantly inhibit KDR kinase at concentrations of 50 micromolar or below. Some compounds of this invention also significantly inhibit other PTKs such as lck at concentrations of 50 micromolar or below.

Cdc2/Cyclin B source

The human recombinant enzyme and assay buffer may be obtained commercially (New England Biolabs, Beverly, MA. USA) or purified from known natural or recombinant sources using conventional methods.

Cdc2/Cyclin B Assay

The protocol used was that provided with the purchased reagents with minor modifications. In brief, the reaction was carried out in a buffer consisting of 50mM Tris pH 7.5, 100mM NaCl, 1mM EGTA, 2mM DTT, 0.01% Brij, 5% DMSO and 10mM $MgCl_2$ (commercial buffer) supplemented with fresh 300 μM ATP (31 μCi/ml) and 30 μg/ml histone type IIIss final concentrations. A reaction volume of 80μL, containing units of enzyme, was run for 20 minutes at 25 degrees C in the presence or absence of inhibitor. The reaction was terminated by the addition of 120μL of 10% acetic acid. The substrate was separated from unincorporated label by spotting the mixture on phosphocellulose paper, followed by 3 washes of 5 minutes each with 75mM phosphoric acid. Counts were measured by a betacounter in the presence of liquid scintillant.

Certain compounds of this invention significantly inhibit cdc2 at concentrations below 50 uM.

PKC kinase source

The catalytic subunit of PKC may be obtained commercially (Calbiochem).

PKC kinase assay

A radioactive kinase assay was employed following a published procedure (Yasuda, I., Kirshimoto, A., Tanaka, S., Tominaga, M., Sakurai, A., Nishizuka, Y. *Biochemical and Biophysical Research Communication 3*:166, 1220-1227 (1990)). Briefly, all reactions were performed in a kinase buffer consisting of 50 mM Tris-HCl pH7.5, 10mM $MgCl_2$, 2mM DTT, 1mM EGTA, 100 μM ATP, 8 μM peptide, 5% DMSO and ^{33}P ATP (8Ci/mM). Compound and enzyme were mixed in the reaction vessel and the reaction initiated by addition of the ATP and substrate mixture. Following termination of the reaction by the addition of 10 μL stop buffer (5 mM ATP

in 75mM phosphoric acid), a portion of the mixture was spotted on phosphocellulose filters. The spotted samples were washed 3 times in 75 mM phosphoric acid at room temperature for 5 to 15 minutes. Incorporation of radiolabel was quantified by liquid scintillation counting.

Erk2 enzyme source

The recombinant murine enzyme and assay buffer may be obtained commercially (New England Biolabs, Beverly MA. USA) or purified from known natural or recombinant sources using conventional methods.

Erk2 enzyme assay

In brief, the reaction was carried out in a buffer consisting of 50 mM Tris pH 7.5, 1mM EGTA, 2mM DTT, 0.01% Brij, 5% DMSO and 10 mM $MgCl_2$ (commercial buffer) supplemented with fresh 100 μM ATP (31 μCi/ml) and 30μM myelin basic protein under conditions recommended by the supplier. Reaction volumes and method of assaying incorporated radioactivity were as described for the PKC assay (vide *supra*).

In Vitro Models for T-cell Activation

Upon activation by mitogen or antigen, T-cells are induced to secrete IL-2, a growth factor that supports their subsequent proliferative phase. Therefore, one may measure either production of IL-2 from or cell proliferation of, primary T-cells or appropriate T-cell lines as a surrogate for T-cell activation. Both of these assays are well described in the literature and their parameters well documented (in Current Protocols in Immunology, Vol 2, 7.10.1-7.11.2).

In brief, T-cells may be activated by co-culture with allogenic stimulator cells, a process termed the one-way mixed lymphophocyte reaction. Responder and stimulator peripheral blood mononuclear cells are purified by Ficoll-Hypaque gradient (Pharmacia) per directions of the manufacturer. Stimulator cells are mitotically inactivated by treatment with mitomycin C (Sigma) or gamma irradiation. Responder and stimulator cells are co-cultured at a ratio of two to one in the presence or absence of the test

compound. Typically 10^5 responders are mixed with 5×10^4 stimulators and plated (200 μl volume) in a U bottom microtiter plate (Costar Scientific). The cells are cultured in RPMI 1640 supplemented with either heat inactivated fetal bovine serum (Hyclone Laboratories) or pooled human AB serum from male donors, 5×10^{-5} M 2-mercaptoethanol and 0.5% DMSO, The cultures are pulsed with 0.5 μCi of ^{3}H thymidine (Amersham) one day prior to harvest (typically day three). The cultures are harvested (Betaplate harvester, Wallac) and isotope uptake assessed by liquid scintillation (Betaplate, Wallac).

The same culture system may be used for assessing T-cell activation by measurement of IL-2 production. Eighteen to twenty-four hours after culture initiation, the supernatants are removed and the IL-2 concentration is measured by ELISA (R and D Systems) following the directions of the manufacturer.

In-vivo Models of T-Cell Activation

The *in vivo* efficacy of compounds can be tested in animal models known to directly measure T-cell activation or for which T-cells have been proven the effectors. T-cells can be activated *in vivo* by ligation of the constant portion of the T-cell receptor with a monoclonal anti-CD3 antibody (Ab). In this model, BALB/c mice are given 10μg of anti-CD3 Ab intraperitoneally two hours prior to exsanguination. Animals to receive a test drug are pre-treated with a single dose of the compound one hour prior to anti-CD3 Ab administration. Serum levels of the proinflammatory cytokines interferon-γ (IFN- γ) and tumor necrosis factor-α(TNF-α), indicators of T-cell activation, are measured by ELISA. A similar model employs *in vivo* T-cell priming with a specific antigen such as keyhole limpet hemocyanin (KLH) followed by a secondary *in vitro* challenge of draining lymph node cells with the same antigen. As previously, measurement of cytokine production is used to assess the activation state of the cultured cells. Briefly, C57BL/6 mice are immunized subcutaneously with 100 μg KLH emulsified in complete Freund's adjuvant (CFA) on day zero. Animals are pre-treated with the compound one day prior to immunization and subsequently on days one, two and three post

immunization. Draining lymph nodes are harvested on day 4 and their cells cultured at 6 x 10^6 per ml in tissue culture medium (RPMI 1640 supplemented with heat inactivated fetal bovine serum (Hyclone Laboratories) 5 x 10^{-5} M 2-mercaptoethanol and 0.5% DMSO) for both twenty-four and forty-eight hours. Culture supernatants are then assessed for the autocrine T-cell growth factor Interleukin-2 (IL-2) and/or IFN-γ levels by ELISA.

Lead compounds can also be tested in animal models of human disease. These are exemplified by experimental auto-immune encephalomyelitis (EAE) and collagen-induced arthritis (CIA). EAE models which mimic aspects of human multiple sclerosis have been described in both rats and mice (reviewed FASEB J. 5:2560-2566, 1991; murine model: Lab. Invest. 4(3):278, 1981; rodent model:J. Immunol 146(4):1163-8, 1991). Briefly, mice or rats are immunized with an emulsion of myelin basic protein (MBP), or neurogenic peptide derivatives thereof, and CFA. Acute disease can be induced with the addition of bacterial toxins such as *bordetella pertussis.* Relapsing/remitting disease is induced by adoptive transfer of T-cells from MBP/ peptide immunized animals.

CIA may be induced in DBA/1 mice by immunization with type II collagen (J. Immunol:142(7):2237-2243). Mice will develop signs of arthritis as early as ten days following antigen challenge and may be scored for as long as ninety days after immunization. In both the EAE and CIA models, a compound may be administered either prophylactically or at the time of disease onset. Efficacious drugs should delay disease onset or reduce severity and/or incidence.

Certain compounds of this invention which inhibit one or more angiogenic receptor PTK, and/or a protein kinase such as lck involved in mediating inflammatory responses can reduce the severity and incidence of arthritis in these models.

Compounds can also be tested in mouse allograft models, either skin (reviewed in Ann. Rev. Immunol., 10:333-58, 1992; Transplantation: 57(12): 1701-17D6, 1994) or heart (Am.J.Anat.:113:273, 1963). Briefly, full thickness skin grafts are transplanted

from C57BL/6 mice to BALB/c mice. The grafts are examined daily, beginning at day six, for evidence of rejection. In the mouse neonatal heart transplant model, neonatal hearts are ectopically transplanted from C57BL/6 mice into the ear pinnae of adult CBA/J mice. Hearts start to beat four to seven days post transplantation and rejection may be assessed visually using a dissecting microscope to look for cessation of beating.

Cellular Receptor PTK Assays

The following cellular assay was used to determine the level of activity and effect of the different compounds of the present invention on KDR/VEGFR2. Similar receptor PTK assays employing a specific ligand stimulus can be designed along the same lines for other tyrosine kinases using techniques well known in the art.

VEGF-Induced KDR Phosphorylation in Human Umbilical Vein Endothelial Cells (HUVEC) as Measured by Western Blots:

1. HUVEC cells (from pooled donors) were purchased from Clonetics (San Diego, CA) and cultured according to the manufacturer directions. Only early passages (3-8) were used for this assay. Cells were cultured in 100 mm dishes (Falcon for tissue culture; Becton Dickinson; Plymouth, England) using complete EBM media (Clonetics).

2. For evaluating a compound's inhibitory activity, cells were trypsinized and seeded at $0.5\text{-}1.0 \times 10^5$ cells/well in each well of 6-well cluster plates (Costar; Cambridge, MA).

3. 3-4 days after seeding, plates were 90-100% confluent. Medium was removed from all the wells, cells were rinsed with 5-10ml of PBS and incubated 18-24h with 5ml of EBM base media with no supplements added (i.e., serum starvation).

4. Serial dilutions of inhibitors were added in 1ml of EBM media (25μM, 5μM, or 1μM final concentration to cells and incubated for one hour at 37 C. Human recombinant $VEGF_{165}$ (R & D Systems) was then added to all the wells in 2 ml of EBM medium at a final concentration of 50ng/ml and incubated at 37 C for 10 minutes. Control cells untreated or treated with VEGF only were used to assess background phosphorylation and phosphorylation induction by VEGF.

All wells were then rinsed with 5-10ml of cold PBS containing 1mM Sodium Orthovanadate (Sigma) and cells were lysed and scraped in 200µl of RIPA buffer (50mM Tris-HC1) pH7, 150mM NaCl, 1% NP-40, 0.25% sodium deoxycholate, 1mM EDTA) containing protease inhibitors (PMSF 1mM, aprotinin 1µg/ml, pepstatin 1µg/ml, leupeptin 1µg/ml, Na vanadate 1mM, Na fluoride 1mM) and 1µg/ml of Dnase (all chemicals from Sigma Chemical Company, St Louis, MO). The lysate was spun at 14,000 rpm for 30min, to eliminate nuclei.

Equal amounts of proteins were then precipitated by addition of cold (-20 C) Ethanol (2 volumes) for a minimum of 1 hour or a maximum of overnight. Pellets were reconstituted in Laemli sample buffer containing 5% -mercaptoethanol (BioRad; Hercules, CA) and boiled for 5min. The proteins were resolved by polyacrylamide gel electrophoresis (6%, 1.5mm Novex, San Deigo, CA) and transferred onto a nitrocellulose membrane using the Novex system. After blocking with bovine serum albumin (3%), the proteins were probed overnight with anti-KDR polyclonal antibody (C20, Santa Cruz Biotechnology; Santa Cruz, CA) or with anti-phosphotyrosine monoclonal antibody (4G10, Upstate Biotechnology, Lake Placid, NY) at 4 C. After washing and incubating for 1 hour with HRP-conjugated $F(ab)_2$ of goat anti-rabbit or goat-anti-mouse IgG the bands were visualized using the emission chemiluminescience (ECL) system (Amersham Life Sciences, Arlington Height, IL).
Certain examples of the present invention significantly inhibit cellular VEGF-induced KDR tyrosine kinase phosphorylation at concentrations of less than 50 µM.

In vivo Uterine Edema Model

This assay measures the capacity of compounds to inhibit the acute increase in uterine weight in mice which occurs in the first few hours following estrogen stimulation. This early onset of uterine weight increase is known to be due to edema caused by increased permeability of uterine vasculature. Cullinan-Bove and Koss (*Endocrinology* (1993), *133*:829-837) demonstrated a close temporal relationship of estrogen-stimulated uterine edema with increased expression of VEGF mRNA in the

uterus. These results have been confirmed by the use of neutralizing monoclonal antibody to VEGF which significantly reduced the acute increase in uterine weight following estrogen stimulation (WO 97/42187). Hence, this system can serve as a model for *in vivo* inhibition of VEGF signalling and the associated hyperpermeability and edema.

Materials: All hormones were purchased from Sigma (St. Louis, MO) or Cal Biochem (La Jolla, CA) as lyophilized powders and prepared according to supplier instructions.

Vehicle components (DMSO, Cremaphor EL) were purchased from Sigma (St. Louis, MO).

Mice (Balb/c, 8-12 weeks old) were purchased from Taconic (Germantown, NY) and housed in a pathogen-free animal facility in accordance with institutional Animal Care and Use Committee Guidelines.

Method:

Day 1: Balb/c mice were given an intraperitoneal (i.p.) injection of 15 units of pregnant mare's serum gonadotropin (PMSG).

Day 3: Mice received 15 units of human chorionic gonadotropin (hCG) i.p.

Day 4: Mice were randomized and divided into groups of 5-10. Test compounds were administered by i.p., i.v. or p.o. routes depending on solubility and vehicle at doses ranging from 1-100 mg/kg. Vehicle control group received vehicle only and two groups were left untreated.

Thirty minutes later, experimental, vehicle and 1 of the untreated groups were given an i.p. injection of 17 -estradiol (500 μg/kg). After 2-3 hours, the animals were sacrificed by CO_2 inhalation. Following a midline incision, each uterus was isolated and removed by cutting just below the cervix and at the junctions of the uterus and oviducts. Fat and connective tissue were removed with care not to disturb the integrity of the uterus prior to weighing (wet weight). Uteri were blotted to remove fluid by pressing

between two sheets of filter paper with a one liter glass bottle filled with water. Uteri were weighed following blotting (blotted weight). The difference between wet and blotted weights was taken as the fluid content of the uterus. Mean fluid content of treated groups was compared to untreated or vehicle treated groups. Significance was determined by Student's test. Non-stimulated control group was used to monitor estradiol response.

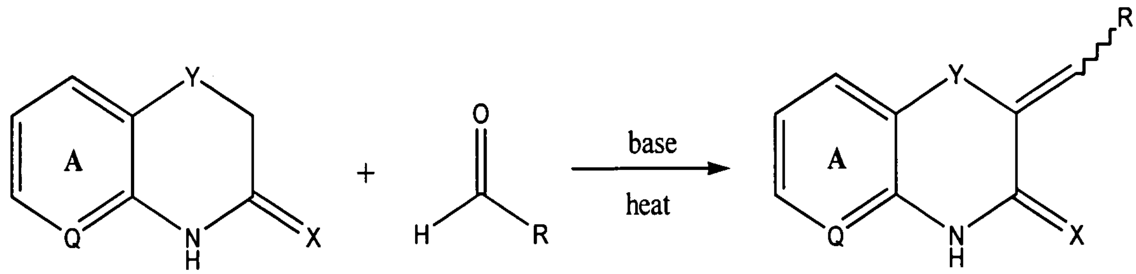
Results demonstrate that certain compounds of the present invention inhibit the formation of edema when administered systemically by various routes.

Certain compounds of this invention which are inhibitors of angiogenic receptor tyrosine kinases can also be shown active in a Matrigel implant model of neovascularization. The Matrigel neovascularization model involves the formation of new blood vessels within a clear "marble" of extracellular matrix implanted subcutaneously which is induced by the presence of proangiogenic factor producing tumor cells (for examples see: Passaniti, A., *et al*, Lab. Investig. (1992), 67(4), 519-528; Anat. Rec. (1997), 249(1), 63-73; Int. J. Cancer (1995), 63(5), 694-701; Vasc. Biol. (1995), 15(11), 1857-6). The model preferably runs over 3-4days and endpoints include macroscopic visual/image scoring of neovascularization, microscopic microvessel density determinations, and hemoglobin quantitation (Drabkin method) following removal of the implant versus controls from animals untreated with inhibitors. The model may alternatively employ bFGF or HGF as the stimulus.

Certain compounds of this invention which inhibit one or more oncogenic, protooncogenic, or proliferation-dependent protein kinases, or angiogenic receptor PTK also inhibit the growth of primary murine, rat or human xenograft tumors in mice, or inhibit metastasis in murine models.

EXEMPLIFICATIONS

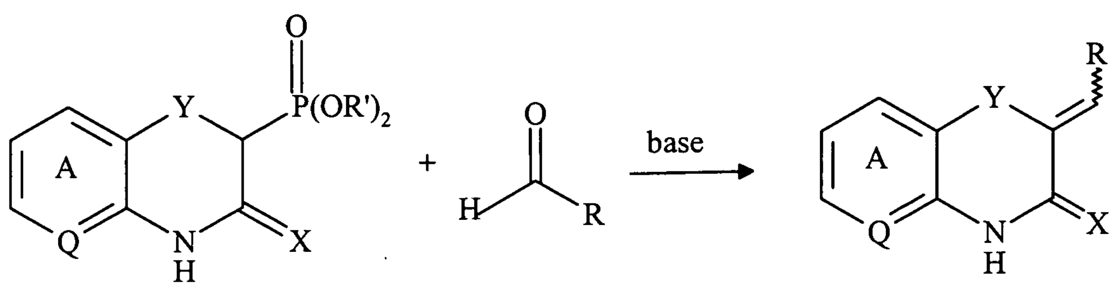
The core structure of the compounds of the invention was synthesized via a base catalyzed aldol condensation followed by an elimination reaction. Scheme I is a general representation of this reaction.



VII. VIII. IX.

Scheme I. General synthesis of common core structure.

Alternatively, the core structure of the compound of the invention was synthesized via a Wadsworth-Emmons reaction, as represented in Scheme II.



X. VIII. IX.

Scheme II. General synthesis of common core structure

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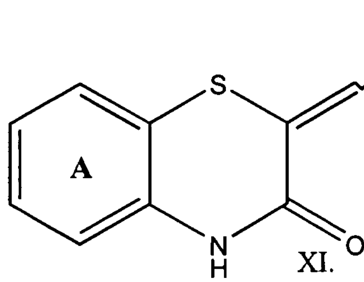
I. (Pyrrol-2-yl)methylene Benzothiazinones (XI).



XI.

The following (pyrrol-2-yl)methylene benzothiazinones (Examples 1-25) were synthesized according to Schemes I and/or II.

Example 1: Synthesis of (Z)-2[(Pyrrol-2-yl)methylene]-2H-1,4-benzothiazin-3(4H)-one:

Sodium methoxide (0.28 g, 5.2 mmol) was added to a solution of 2H-1,4-benzothiazin-3(4H)-one (0.60 g, 4 mmol) and pyrrol-2-carboxaldehyde (0.49 g, 5.2 mmol) in dry N,N-dimethylformamide (3.5 ml) (hereinafter "DMF"). The mixture was heated at 120°C for 6.5 h, allowed to cool and poured into water (60 ml). The precipitate was collected by filtration and washed with water. The precipitate was dissolved in ethyl acetate and the insoluble black residue was filtered out. The filtrate was concentrated, then chromatographed on a silica column using a gradient of 100% dichloromethane to (100 : 1) dichloromethane:ethanol as the mobile phase. The first eluted product was the (E)-isomer.

Example 12: Synthesis of (Z)-7-Amino-2-[(pyrrol-2-yl)methylene]-2H-1,4-benzothiazin-3(4H)one:

A catalytic amount of Raney nickel was added portionwise with stirring to a mixture of (Z)-7-nitro-2-[(pyrrol-2-yl)methylene]-2H-1,4-benzothiazin-3(4H)-one (Example 5) (0.43 g, 1.5 mmol) and hydrazine hydrate (98%) (0.8 ml) in ethanol (20 ml). The reaction mixture heated under reflux for 5.5 hours, then filtered and the solvent

removed in vacuo. The product was purified by silica gel chromatography using a gradient of (98 : 2) to (95 : 5) toluene : ethanol as the mobile phase.

Example 13: Synthesis of 2-[(4,5-Dimethylpyrrol-2-yl)methylene]-2H -1,4-benzothiazin-3(4H)-one:

4,5-Dimethylpyrrole-2-carboxaldehyde (0.27 g, 2.19 mmol) was added to a solution of 2H-1,4-benzothiazin-3(4H)-one (0.36 g, 2.19 mmol) and sodium methoxide (0.118 g, 2.19 mmol) in dry DMF (2 ml). The mixture was heated at 120°C for 48 h, allowed to cool and poured into ice-water (50 ml). The precipitated solid was collected by filtration, washed with water, then dissolved in ethanol. The insoluble black residue was filtered out and the filtrate was concentrated to dryness under reduced pressure. The product was purified by silica gel chromatography using (98 : 2) dichloromethane: methanol as the mobile phase.

Example 17: Synthesis of (Z)-2-{[1-(4-hydroxybutyl)pyrrol-2-yl]methylene}-2H-1,4-benzothiazin-3(4H)-one:

Sodium methoxide (0.07 g, 1.3 mmol) was added to a solution of 2-diethylphosphonyl-2H-1,4-benzothiazin-3(4H)-one (0.30 g, 1.0 mmol) and 1-(4-hydroxybutyl)pyrrol-2-carboxaldehyde (0.17 g, 1.0 mmol) in methanol (4 ml). The mixture was stirred at room temperature for 48 h. The precipitate was collected by filtration and washed with cold methanol . Yield: 0.31 g (41%).

Example 24: Synthesis of 2-{[1-(N-(3-dimethylaminopropyl)carbamoylmethyl) pyrrol-2-yl]methylene}-2H-1,4-benzothiazin-3(4H)-one:

A mixture of 2-{[1-(ethoxycarbonylmethyl)pyrrol-2-yl]methylene}-2H-1,4-benzothiazin-3(4H)-one (example 21) (0.20 g, 0.6 mmol) and 3-dimethylamino propylamine (1.5 ml) was heated at 100°C for 1 hour. After cooling, ethanol (5 ml) was

added, the mixture was stirred and the precipitate was filtered off and washed with ethanol. Yield: 0.21 g.

Table 1 lists other compounds synthesized having structural formula XI. Examples 1-11 and 14-16 were synthesized as described in Example 1 using an appropriately substituted 2H-1,4-benzothiazin-3(4H)-one and an appropriately substituted pyrrole-2-carboxaldehyde. Example 12 required an additional hydrogenation step, which is described above. The reaction conditions in Example 13 differed slightly from those in Example 1, and therefore, they have also been described above. Examples 17-21 were synthesized as described in Example 17 using an appropriately substituted pyrrole-2-carboxaldehyde. Examples 23-25 were obtained from Example 21 and the appropriate amine as described in Example 24.. Table 2 lists the physical data for compounds in Table 1.

Table 1: Compounds synthesized having structural formula XI.

Example	Substituent on Ring A	Substituent on Ring B	Chromatographic Mobile Phase	% Yield (E)-Isomer	% Yield (Z)-Isomer
1	none	none	100 % CH_2Cl_2 to (100 : 1) CH_2Cl_2 : EtOH	trace	49
2	7-OCH_3	none	100 % CH_2Cl_2 to (100 : 1) CH_2Cl_2 : EtOH	14	30
3	6-OCF_3	none	100 % CH_2Cl_2 to (100 : 1) CH_2Cl_2 : EtOH	5	33
4	7-CH_3	none	100 % CH_2Cl_2 to (100 : 1) CH_2Cl_2 : EtOH	5	42
5	7-NO_2	none	100 % CH_2Cl_2 to (100 : 1) CH_2Cl_2 : EtOH	4	40
6	7-Cl	none	100 % CH_2Cl_2 to (100 : 1) CH_2Cl_2 : EtOH	4	60
7	6-Cl	none	100 % CH_2Cl_2 to (100 : 1) CH_2Cl_2 : EtOH	5	42
8	6-CH_3	none	100 % CH_2Cl_2 to (100 : 1) CH_2Cl_2 : EtOH	6	24
9	7-OH	none	100 % CH_2Cl_2 to (100 : 1) CH_2Cl_2 : EtOH	1	23

10	none	$5\text{-}CH_3$	(7 : 3) toluene : ethyl acetate	3	62
11	none	3,5-dimethyl	(9 : 1) toluene : ethyl acetate	3	10
12	$7\text{-}NH_2$	none	(98 : 2) to (95 : 5) toluene : ethyl acetate	not applicable	67
13	none	4,5-dimethyl	(98 :2) $CH_2Cl_2 : CH_3OH$	9 % as a mixture of isomers	9 % as a mixture of isomers
14	none	4-ethyl-3,5-dimethyl	(95:5) Toluene:ethyl acetate	40% as a mixture of isomers	40% as a mixture of isomers
15	none	4-ethoxy carbonyl-3,5-dimethyl	(9:1) to (8:2) Hexane:ethyl acetate	11	32
16	none	1-methyl	NA	-	88
17	none	1-(4-hydroxybutyl)	NA	-	41
18	none	1-(2-hydroxyethyl)	NA	-	81
19	none	1-(3-dimethylaminopropyl)	NA	-	71
20	none	4-bromo	NA	-	92
21	none	1-ethoxycarbonyl methyl	NA	-	48
22 (potassium salt)	none	1-carboxymethyl	NA	-	85
23	none	1-[N-(2-morpholinoethyl) carbamoyl methyl]	NA	-	88
24	none	1-[N-(3-dimethylaminopropyl)carbamoyl methyl]	NA	-	91
25	none	1-[(4-methyl piperazin-1-yl)carbonylmethyl]	NA	-	52

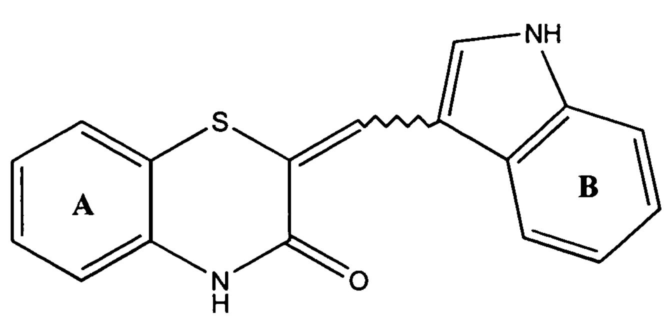
Table 2: Physical data for compounds synthesized having structural formula XI.

Example	Mp. (°C)	Elemental analysis					
		Carbon		Hydrogen		Nitrogen	
		calculated	found	calculated	found	calculated	found
1 (E)-isomer	NA	NA	NA	NA	NA	NA	NA
1 (Z)-isomer	248-50	64.44	64.59	4.16	4.22	11.56	11.48
2 (E)-isomer	190-2	61.75	61.52	4.44	4.48	10.29	10.13
2 (Z)-isomer	258-60	61.75	62.02	4.44	4.48	10.29	10.04
3 (E)-isomer	207-9	54.19	54.13	2.92	3.19	9.03	8.97
3 (Z)-isomer	272-3	54.19	54.61	2.92	3.11	9.03	8.86
4 (E)-isomer	211-2	65.60	65.30	4.72	4.43	10.93	10.82
4 (Z)-isomer	248-9	65.60	65.68	4.72	4.80	10.93	10.86
5 (E)-isomer	258-60	54.35	54.37	3.16	3.37	14.63	14.78
5 (Z)-isomer	330-40	54.35	54.43	3.16	3.56	14.63	14.67
6 (E)-isomer	243-6	NA	NA	NA	NA	NA	NA
6 (Z)-isomer	244-5	56.42	56.47	3.28	3.13	10.12	9.92
7 (E)-isomer	235-8	NA	NA	NA	NA	NA	NA
7 (Z)-isomer	283-5	56.42	56.70	3.28	3.64	10.12	9.82
8 (E)-isomer	220-2	NA	NA	NA	NA	NA	NA
8 (Z)-isomer	275-7	65.60	65.97	4.72	4.72	10.93	10.65
9 (E)-isomer	220-3	NA	NA	NA	NA	NA	NA
9 (Z)-isomer	247-9	60.45	60.17	3.90	3.88	10.85	10.51
10 (E)-isomer	211-13	65.60	65.46	4.72	4.44	10.93	10.48
10 (Z)-isomer	226-8	65.60	66.02	4.72	4.92	10.93	10.72
11 (E)-isomer	210-15	66.64	66.23	5.22	4.90	10.36	10.29
11 (Z)-isomer	218-20	66.64	67.09	5.22	5.17	10.36	10.19

12 (Z)-isomer (0.2 EtOH)[1]	225-30	60.39	60.41	4.61	4.58	15.76	15.75
13 mixture of isomers (0.1 toluene)[1]	246-48	67.45	67.01	5.34	5.04	10.02	9.80
14 mixture of isomers	170-184	68.43	68.58	6.08	6.10	9.39	9.50
15 (E)-isomer	221-3	63.14	63.16	5.30	5.27	8.18	8.14
15 (Z)-isomer	230-2	63.14	63.17	5.30	5.27	8.18	8.14
16 (Z)-isomer	222-4	65.60	65.69	4.72	4.60	10.93	10.93
17 (Z)-isomer	140-5	64.94	65.12	5.77	5.47	8.91	8.84
18 (Z)-isomer	182	62.92	62.78	4.93	5.23	9.78	9.76
19 (Z)-isomer	139-41	66.03	65.94	6.46	6.21	12.83	12.75
20 (Z)-isomer	>340	48.61	48.80	2.82	2.64	8.72	8.64
21 (Z)-isomer	195-7	62.18	62.23	4.91	4.95	8.53	8.48
22 (Z)-isomer ($1H_2O$)[1]	225-7	50.55	50.92	3.68	3.66	7.86	7.86
23 (Z)-isomer	245-8	61.15	61.06	5.86	5.90	13.58	13.35
24 (Z)-isomer	229-30	62.48	62.42	6.29	6.34	14.57	14.34
25 (Z)-isomer	237-9	62.81	62.43	5.80	5.82	14.65	14.38

1) The molecular weight calculated for the elemental analysis includes the solvent in the amount indicated.

II. (Indol-3-yl)methylene Benzothiazinones (XII).



XII.

The following (indol-3-yl)methylene benzothiazinones (Examples 26-122) were synthesized according to Schemes I and/or II.

Example 26: Synthesis of (Z)-2-[(Indol-3-yl)methylene]-2H-1,4-benzothiazin-3(4H)-one:

A solution of 2H-1,4-benzothiazin-3(4H)-one (1.65 g, 10 mmol) and indole-3-carboxaldehyde (1.45 g, 10 mmol) in piperidine (30 ml) was heated under reflux for 5 days. The solvent was removed *in vacuo*, ethanol (20 ml) was added to the residue and the solid was filtered off. This solid was boiled in ethanol (20 ml) and filtered hot to give a yellow solid.

Example 28: 2-[(indol-3-yl)methylene]-7-methyl-2H-1,4-benzothiazin-3(4H)-one

Sodium methoxide (0.28 g, 5.2 mmol) was added in one portion to a solution of 7-methyl-2H-1,4-benzothiazin-3(4H)-one (0.72 g, 4.0 mmol) and indole-3-carboxaldehyde (0.88 g, 6.0 mmol) in dry DMF (4 mL) . The mixture was heated for 48 h at 140°C, allowed to cool, then poured into water (60 ml). The precipitate was collected by filtration and washed with water. The precipitate was then refluxed with toluene (100 ml) and filtered hot to give a yellow solid which was purified by silica gel chromatography using a gradient of (100 : 1) to (100 : 20) toluene : ethanol as the mobile phase.

Example 39 (salt): Synthesis of 2-{[1-(N,N-Dimethyl-3-aminopropyl)indol-3-yl]methylene}-2H-1,4-benzothiazin-3(4H)-one methanesulfonate:

Methanesulfonic acid (0.127 g, 1.3 mmol) was added to a suspension of 2-{[1-N,N-dimethyl-3-aminopropyl)indol-3-yl]methylene}-2H-1,4-benzothiazin-3(4H)-one (Example 36) (0.5 g, 1.3 mmol) in dry dichloromethane (40 ml). The mixture was stirred at room temperature overnight, and the precipitated solid was collected by filtration, washed with dichloromethane and diethylether, then dried under nitrogen to give the product.

Example 40: Synthesis of 7-Hydroxy-2-[(indol-3-yl)methylene]-2H-1,4-benzothiazin-3(4H)-one:

Sodium methoxide (0.54 g, 10 mmol) was added in one portion to a solution of 7-hydroxy-2H-1,4-benzothiazin-3(4H)-one (0.91 g, 5 mmol) and indole-3-carboxaldehyde (1.09 g, 7.5 mmol) in dry DMF (5 ml). The mixture was heated at 140°C for 48 h, allowed to cool and poured into ice water (60 ml). The solid was collected by filtration. The filtrate was acidified to pH=2 with 10% hydrochloric acid and the precipitated solid was collected by filtration. Both precipitates were put together, boiled with toluene and filtered hot to give a solid which was purified by silica gel chromatography using a gradient of (9 : 1) to (8 : 2) n-hexane/ethanol as the mobile phase.

Example 41: Synthesis of 7-Amino-2-[(indol-3-yl)methylene]-2H-1,4-benzothiazin-3(4H)-one:

A catalytic amount of Raney nickel was added portionwise with stirring to a mixture of 7-nitro-2-[(indol-3-yl)methylene]-2H-1,4-benzothiazin-3(4H)-one (see Example 31) (0.39 g, 1.16 mmol) and hydrazine hydrate (98%) (0.60 ml) in ethanol (15 ml). The reaction mixture was refluxed for 5 h, then filtered hot. The solid residue was boiled with ethanol (100 ml) and filtered hot. The combined filtrates were brought to dryness *in vacuo* and chromatographed on silica gel using a gradient of (9 :1) to (8 :2) dichloromethane : ethanol as the mobile phase to afford 0.17 g (35%) product.

Example 42: Synthesis of 1-{3-Oxo-2-[(indol-3-yl)methylene]-2H-1,4-benzothiazin-7-yl}-3-*tert*-butyl urea

A mixture of 7-amino-2-[(indol-3-yl)methylene]-2H-1,4-benzothiazin-3(4H)-one (see Example 38) (0.17 g, 0.55 mmol) and tert-butyl isocyanate (0.17 g, 1.75 mmol) in dry DMF (1 ml) was stirred at room temperature for 4 days. The reaction was poured into water (25 ml) and the precipitated solid was collected by filtration. The precipitate was purified by silica gel chromatography using a gradient of (9 : 1) to (4 : 6) toluene : ethyl acetate as the mobile phase.

Example 60: Synthesis of 2-{[1-(Carbamoylmethyl)indol-3-yl]methylene}-2H-1,4-benzothiazin-3(4H)-one:

Sodium methoxide (0.12 g, 2.22 mmol) was added to a mixture of 2-diethylphosphonyl-2H-1,4-benzothiazin-3(4H)-one (0.30 g, 1.0 mmol) and 1-carbamoylmethylindole-3-carboxaldehyde (0.20 g, 1.0 mmol) in methanol (20 ml). The reaction mixture was heated at reflux for 6 hours. After cooling, the precipitate was filtered and washed with methanol and water. Yield: 0.24 g (69%).

Example 75: Synthesis of (Z)-2-{{6-[2-(Pyrrolidin-1-yl)ethyloxycarbonyl]indol-3-yl}methylene}-2H-1,4-benzothiazin-3(4H)-one:

To a solution of (Z)-2-[(6-carboxyindol-3-yl)methylene]-2H-1,4-benzothiazin-3(4H)-one (0.5 g, 1.5 mmol) in dry N,N-dimethylformamide (30 ml), 1,1'-carbonyldiimidazol (0.24 g, 1.5 mmol) was added under nitrogen atmosphere, and the mixture was heated at 40°C for 1 h. Then N-(2-hydroxyethyl)pyrrolidine (0.34 g, 2.95 mmol) and DBU (1,8-diazabicyclo[5,4,0]undec-7-ene (0.23 ml, 1.5 mmol) were added, and the resulting mixture heated at the same temperature for an additional time of 5 h. The reaction was allowed to cool to room temperature and poured into ice/water. The precipitated solid was filtered off, washed with water and cristallized from N,N-dimethylformamide/water to yield 0.44 g (68%) of the entitled product.

Example 79: Synthesis of (Z)-2-{{6-{N-[2-(Pyrrolidin-1-yl) ethyl]carbamoyl} indol-3-yl}methylene}-2H-1,4-benzothiazin-3(4H)-one:

To a solution of (Z)-2-[(6-carboxyindol-3-yl)methylene]-2H-1,4-benzothiazin-3(4H)-one (0.5 g, 1.5 mmol) in dry N,N-dimethylformamide (30 ml), 1,1'-carbonyldiimidazol (0.24 g, 1.5 mmol) was added under nitrogen atmosphere, and the mixture was heated at 40°C for 1 h. Then N-(2-aminoethyl)pyrrolidine (0.34 g, 2.98 mmol) was added and the mixture heated at the same temperature for an additional time of 20 h. The reaction was allowed to cool to room temperature and the solvent removed under reduced pressure. The residue was treated with water and the yellow precipitate was crystallized from N,N-dimethylformamide/water to yield 0.31 g (48%) of the entitled product.

Example 87: Synthesis of (Z)-2-{{5-[2-(Piperidin-1-yl)ethyloxy]indol-3-yl}methylene}-2H-1,4-benzothiazin-3(4H)-one:

To a solution of (Z)-2[(5-hydroxyindol-3-yl)methylene]-2H-1,4-benzothiazin-3(4H)-one (1.00 g, 3.24 mmol) and 1,1'-(azodicarbonyl)dipiperidine (1.23 g, 4.87 mmol) in dry tetrahydrofurane (40 ml), tributylphosphine (0.98 g, 4.87 mmol) was added under nitrogen atmosphere keeping the mixture at 0-5°C. After 5 min N-(2-hydroxyethyl)piperidine (0.63 g, 4.88 mmol) was added at the same temperature. The cooling bath was removed and the mixture stirred at room temperature for 48 h. Then the solvent was removed under reduced pressure and the residue chromatographed (silica gel, eluent, ethyl acetate : ethanol (90 : 10) to (80 : 20)) to yield 0.2 g (22%) of the entitled product.

Table 3 lists other compounds synthesized having structural formula X. Examples described in Table 3 were synthesized by the method indicated therein. Table 4 lists the physical data for compounds in Table 3.

Table 3: Compounds synthesized having structural formula XII.

Example	Substituent on Ring A	Substituent on Ring B	Chromatographic Mobile Phase	% Yield	Method
26	none	none	NA	14	see Example 26
27	7-Cl	none	NA	18	see Example 26
28	7-CH_3	none	(100 : 1) to (100 : 20) toluene : ethanol	44	see Example 28
29	6-CF_3	none	(100 : 1) to (100 : 20) toluene : ethanol	83	see Example 28
30	6-CH_3	none	(100 : 1) to (100 : 20) toluene : ethanol	36	see Example 28
31	6-Cl	none	(100 : 1) to (100 : 20) toluene : ethanol	42	see Example 28
32	7-OCH_3	none	(100 : 1) to (100 : 20) toluene : ethanol	27	see Example 28
33	6-acetyl-amino	none	(100 : 1) to (100 : 20) toluene : ethanol	35	see Example 28
34	7-NO_2	none	(100 : 1) to (100 : 20) toluene : ethanol	42	see Example 28
35	7-acetyl-amino	none	95 : 5 ethylacetate : ethanol	21	see Example 28
36	none	1-(4-hydroxy-butyl)	98 : 2 dichloromethane : ethanol	34	see Example 28
37	none	5-OCH_3	(100 : 1) to (100 : 20) toluene : ethanol	56	see Example 28
38	none	1-(2-hydroxy-ethyloxymethyl)	95 : 5 toluene : ethanol	30	see Example 28
39	none	1-(N,N-dimethyl-3-aminopropyl)	(100 : 1) to (100 : 20) toluene : ethanol	77	see Example 28
39 (salt)	none	1-(N,N-dimethyl-3-aminopropyl)	NA	81	see Example 39 (salt)
40	7-OH	none	(9 : 1) to (8 : 2) n-hexane : ethanol	27	see Example 40
41	7-NH_2	none	(9 : 1) to (8 : 2) dichloromethane : ethanol	35	see Example 41
42	7-(3-tert-butyl) urea	none	(9 : 1) to (4 : 6) toluene : ethylacetate	50	see Example 42
43	none	6-methoxy-carbonyl	(100 : 1) to (100 : 20) toluene : ethanol	41	see Example 28
44	none	2-CH_3	(8:2) toluene:ethanol	13	see example 28

45	7-OH	1-(2-hydroxy-ethyloxymethyl)	(2:8) toluene:ethyl acetate	5	see example 28
46	none	1-CH_3	NA	46	see example 28
47	none	1-isopropyl	100% CH_2Cl_2 to (95:5) CH_2Cl_2:ethyl acetate	59	see example 28
48	none	1-(2-hydroxy-N,N-dimethyl-3-aminopropyl)	(95:5) to (7:3) toluene-ethanol	14	see example 28
49	7-benzoyl amino	none	NA	32	*
50	7-chloroacetyl amino	none	(7:3) to (7:2) CH_2Cl_2:ethyl acetate	66	*
51	7-(morpholin-4-yl) acetylamino	none	NA	67	*
52	7-propenoyl amino	none	(100:3) CH_2Cl_2:methanol	53	*
53	7-[3-morpholin-4-yl) propionamido]	none	(100:3) to (100:5) CH_2Cl_2:ethanol	NA	*
54	none	5-hydroxy	(95:5) to (7:3) toluene:ethanol	80	*
55	none	6-carboxy	NA	45	*
56	none	5-amino-2-methyl	(95:5) Cl_2CH_2:methanol	73	*
57	none	6-(2-Dimethylaminoethyl oxycarbonyl)	(9 : 1) to (8 : 2) CH_2Cl_2 : methanol	12	see example 75
58	none	6-(2-morpholino ethyloxycarbonyl)	(9 : 1) CH_2 Cl_2 : ethanol	25	see example 75
59	none	6-(3-dimethyl -aminopropyl carbamoyl)	NA	50	see example 79
60	none	1-carbamoyl methyl	NA	69	see example 60
61	none	1,2-(3-hydroxymethyl) tetramethylene	NA	39	see example 60
62	none	1-ethoxycarbonyl methyl	NA	47	see example 17
63	none	4-methoxycarbonyl	NA	78	see example 60

64	none	1-(2-ethoxycarbonyl ethyl)	NA	49	see example 17
65	none	7-methoxy carbonyl	NA	61	see example 17
66	none	2-ethoxycarbonyl	NA	66	see example 17
67	none	1-cyclopentyl	NA	52	see example 60
68	none	1-(3-tetrahydro furanyl)	NA	59	see example 60
69	none	6-N,N-dimethyl aminosulfonyl	NA	72	see example 17
70	none	5-acetyl aminomethyl	(95 : 5) to (80 : 20) dichloromethane: ethanol	25	see example 60
71	none	1-(diethyl carbamoyl)	(95 : 5) toluene : ethanol	27	see example 60
72	none	5-hydroxy-1-methyl	NA	85	see example 60
73	none	6-methoxy	NA	86	see example 60
74	none	6-hydroxy	NA	78	*
75	none	6-[2-(pyrrolidin-1-yl)ethyloxy carbonyl]	NA	68	see example 75
76	none	6-(2-dimethylamino ethyloxy carbonyl)-1-methyl	(90 : 10) to (80 : 20) Cl_2CH_2 : methanol	3	see example 75
77	none	6-(3-dimethylamino propyloxy carbonyl)	(40 : 60) Cl_2CH_2 : methanol	64	see example 75
78 sodium salt	none	6-carboxy-1-(2-hydroxyethyl)	NA	46	see example 75
79	none	6-{N-[2-(pyrrolidin-1-yl)ethyl] carbamoyl}	NA	48	see example 79
80	none	6-[N-(2-morpholinoethyl) carbamoyl]	(95 : 5) Cl_2CH_2 : methanol	40	see example 79
81	none	6-[N-(2-dimethylamino ethyl)carbamoyl]	(80 : 20) Cl_2CH_2 : methanol	10	see example 79

82	none	6-{N-[3-(4-methylpiperazin-1-yl)propyl] carbamoyl}	NA	73	see example 79
83	none	6-{N-[2-(piperidin-1-yl) ethyl]carbamoyl}	NA	64	see example 79
84	none	6-[N-(2-dimethylamino propyl) carbamoyl]	NA	33	see example 79
85	none	6-{N-[2-(dimethylamino ethyl)-N-methyl] carbamoyl}	NA	38	see example 79
86	none	6-[(4-methylpiperazin-1-yl)carbonyl]	NA	53	see example 79
87	none	5-[2-(piperidin-1-yl)ethyloxy]	(90 : 10) to (80 : 20) ethyl acetate : ethanol	22	see example 87
88	none	5-(3-dimethylamino propyloxy)	(90 : 10) Cl_2CH_2 : methanol	12	see example 87
89	none	5-(2-morpholino ethyloxy)	(95 : 5) toluene : ethanol	44	see example 87
90	none	5-(3-dimethylamino propyloxy)-1-(isopropyloxy carbonyl)	(90 : 10) Cl_2CH_2 : methanol	5	see example 87
91	none	5-(3-dimethylamino propyloxy)-1-methyl	(90 : 10) Cl_2CH_2 : methanol	28	see example 87
92	none	5-(2-morpholinoethyloxy)-1-methyl	(80 : 20) to (0 : 100) hexane : ethylacetate	28	see example 87
93	none	5-[2-(pyrrolidin-1-yl)ethyloxy]	(100 : 0) to (0 : 100) ethyl acetate : methanol	21	see example 87
94	none	5-(2-dimethylamino-ethyloxy)	(95 : 5) to (0 : 100) ethyl acetate : ethanol	27	see example 87

95	none	6-(3-dimethylamino propyloxy)	(85 : 15) Cl_2CH_2 : methanol	28	see example 87
96	none	6-(2-morpholinoethyloxy)	(100 : 0) to (95 : 5) ethyl acetate : ethanol	43	see example 87
97	none	6-[2-(piperidin-1-yl)ethyloxy]	(90 : 10) to (60 : 40) toluene : methanol	28	see example 87
98	none	6-[2-(pyrrolidin-1-yl)ethyloxy	(100 : 0) to 60 : 40) ethyl acetate : methanol	22	see example 87
99	none	6-(2-dimethylamino ethyloxy)	(100 : 0) to (50 : 50) ethyl acetate : ethanol	45	see example 87
100	none	6-[(2-dimethyl amino-2-methyl) propyloxy]	(95 : 5) ethyl acetate : ethanol	46	see example 87
101	none	6-[2-(1-methylpyrrolidin-2-yl)ethyloxy]	(100 : 0) to (0 : 100) ethyl acetate : methanol	30	see example 87
102	none	6-[2-(1-methylpiperidin-3-yl)methyloxy	(100 : 0) to (80 : 20) ethyl acetate : ethanol	39	see example 87
103	none	7-(dimethylaminomethyl)-6-hydroxy	NA	92	*
104	none	7-(dimethylaminomethyl)-6-(2-morpholinoethyloxy)	(90 : 10) to (70 : 30) Cl_2CH_2 : methanol	31	*
105	none	2-methyl-5-(N'-ethylureido)	NA	74	*
106	none	2-methyl-5-(p-toluensulfonyl amino)	(98 : 2) Cl_2CH_2 : methanol	18	*
107	none	6-[(3-dimethyl aminopropyl) aminomethyl]	(40 : 60 : 10) Cl_2CH_2 : methanol : NH_4OH	23	see example 60
108	none	6-[(2-methoxyethyl)aminomethyl]	NA	6.5	see example 60
109	none	1-carboxymethyl	NA	58	*

110	none	1-[N-(2-morpholinoethyl)carbamoyl methyl]	NA	59	see example 24
111	none	1-[N-(2-methoxyethyl) carbamoyl methyl]	NA	83	see example 24
112	none	1-[N-(3-dimethylamino propyl)carbamoyl methyl]	NA	76	see example 24
113	none	1-[N-(2-(2-pyridyl)ethyl) carbamoylmethyl]	NA	83	see example 24
114	none	1-{N-[2-(pyrrolidin-1-yl) ethyl]carbamoylmethyl}	NA	67	see example 24
115	none	7-[N-(3-dimethylamino propyl)carbamoyl]	(1 : 1) dichloromethane : methanol	55	see example 79
116	none	1-(4-methylpiperazin-1-yl)carbonyl methyl	NA	63	see example 79
117	none	1-[N,N-bis(2-N',N'-diethyl aminoethyl) carbamoylmethyl]	(60 : 40) to (40 : 60) ethyl acetate : methanol	44	see example 79
118	none	1-(4-piperidino piperidin-1-yl) carbonylmethyl	(95 : 5) to (90 : 10) dichloromethane : methanol	50	see example 79
119	none	1-[N-(2-N'N'-diethylamino ethyl)-N-methyl] carbamoylmethyl	NA	91	see example 79
120	none	7-carboxy	NA	85	*
121	none	7-(4-methylpiperazin-1-yl)carbonyl	(95 : 5) dichloromethane : methanol	23	see example 79

122	none	7-[4-(2-hydroxyethyl) piperazin-1-yl] carbonyl	(95 : 5) dichloromethane : methanol	17	see example 79

* These compounds were obtained from the corresponding (indol-3-yl) methylene benzothiazinones already described by methods well known for those skilled in the art.

Table 4: Physical data for compounds synthesized having structural formula XII.

Example	Mp. (°C)	Elemental analysis					
		Carbon		Hydrogen		Nitrogen	
		calculated	found	calculated	found	calculated	found
26	> 300	67.8	68.2	4.3	4.15	9.3	9.4
27	> 325	62.5	62.5	3.4	3.4	8.6	8.6
28	298 - 300	70.56	70.01	4.61	4.79	9.14	9.17
29	345 - 6	60.00	59.99	3.08	3.21	7.77	7.57
30 (0.25 H_2O)[1]	303 - 5	69.54	69.43	4.70	4.49	9.01	8.99
31 (0.5 H_2O)[1]	> 350	60.80	61.13	3.60	3.55	8.34	8.71
32	311 - 3	67.06	66.68	4.38	4.68	8.69	8.40
33 (1.0 H_2O)[1]	330 - 4	62.11	62.31	4.66	4.55	11.44	11.27
34	> 350	60.53	59.89	3.29	3.63	12.46	12.38
35	275 - 7	65.31	65.06	4.33	4.50	12.03	12.01
36 (0.25 H_2O)[1]	233 - 5	68.36	68.37	5.60	5.51	7.59	7.53
37 (0.2 DMF)[1]	283 - 5	66.29	66.54	4.61	4.70	9.14	8.91
38 (0.5 H_2O)[1]	210 - 2	63.98	64.34	5.10	5.01	7.46	7.31
39	185 - 7	NA	NA	NA	NA	NA	NA
39 (salt) (1.0 H_2O)[1]	130 - 2	56.19	56.43	5.94	5.53	8.55	8.54
40	293 - 6	66.22	65.83	3.92	4.41	9.08	8.88
41	301 - 6	66.43	65.97	4.26	4.48	13.67	13.45
42	> 330	65.00	64.75	5.45	5.58	13.78	13.60
43	320 - 2	65.13	64.84	4.03	3.95	7.99	7.88

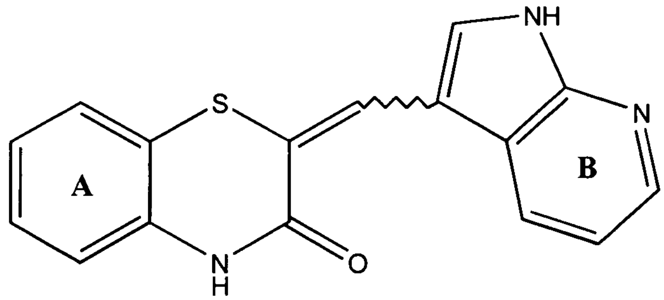
44 (0.2 ethyl acetate)[1]	269-71	69.69	69.93	4.85	4.57	8.64	8.86
45 (0.25 H_2O)[1]	230-2	62.08	62.05	4.82	4.66	7.24	7.16
46	264-6	70.56	70.83	4.61	4.78	9.14	8.97
47	182-4	71.83	71.46	5.43	5.64	8.38	8.16
48 (0.33 H_2O)[1]	198-200	66.14	65.98	5.97	5.92	10.51	10.23
49	>340	70.06	69.73	4.16	4.43	10.21	10.13
50	284-7	59.45	58.99	3.68	3.81	10.95	10.69
51 (0.8 H_2O)[1]	260-2	61.54	61.55	5.30	5.29	12.48	12.31
52	262-75	66.47	66.02	4.18	4.09	11.63	11.50
53 (0.8 H_2O)[1]	241-3	62.27	62.18	5.57	5.40	12.10	11.89
54	306-8	66.21	65.92	3.92	4.21	9.08	8.86
55 (1.8 H_2O)[1]	>350	58.62	58.25	4.00	3.67	7.59	7.44
56 (0.5 H_2O)[1]	242-4	65.43	65.88	4.88	4.88	12.71	13.05
57	255-6	64.85	64.92	5.19	5.27	10.31	9.94
58	310-1	64.12	63.78	5.15	5.44	9.35	9.47
59	279-81	65.69	65.28	5.75	5.62	13.32	13.16
60	330-3	65.31	64.95	4.33	4.53	12.03	11.91
61 (0.4 EtOH)[1]	227-9	69.34	69.14	5.72	5.49	7.09	7.00
62	248-50	66.65	66.34	4.79	4.86	7.40	7.36
63	247-9	65.13	65.14	4.03	4.08	7.99	7.93
64	216-7	67.33	67.13	5.14	5.19	7.14	7.14
65	334-5	65.13	65.20	4.03	4.14	7.99	8.03
66	316-8	64.63	64.30	4.56	4.55	7.54	7.39
67	229-31	73.30	72.70	5.59	5.68	7.77	7.73
68	228-30	69.59	68.92	5.01	5.05	7.73	7.68
69 (0.3 H_2O)[1]	>320	56.36	56.29	4.45	4.35	10.37	10.28
70	262-3	66.10	65.63	4.71	4.86	11.56	11.39
71 (0.3 H_2O)[1]	178-80	66.58	66.91	5.48	5.73	10.59	10.13
72	264-7	67.06	66.68	4.38	4.49	8.69	8.57
73	306-10	67.08	66.91	4.37	4.51	8.69	8.61

74 (0.1 H_2O)[1]	>335	66.21	65.67	3.92	4.27	9.08	9.38
75 (0.25 H_2O)[1]	278-80	65.81	65.80	5.41	5.52	9.59	9.66
76	235-6	64.84	64.96	5.56	5.42	9.86	9.52
77	245-6	65.53	65.32	5.49	5.34	9.97	9.89
78 (2 H_2O)[1]	>350	54.79	55.05	4.36	3.99	6.38	6.28
79 (0.2 H_2O)[1]	303-5	66.09	65.76	5.64	5.53	12.84	12.78
80	296-300	64.27	64.15	5.39	5.68	12.49	12.23
81 (1 H_2O)[1]	285-7	62.24	62.17	5.69	5.55	13.19	12.80
82	270-2	64.44	64.10	6.24	6.15	14.45	14.63
83	314-5	67.24	66.81	5.87	5.98	12.54	12.61
84 (0.9 H_2O)[1]	262-5	63.25	63.51	5.95	5.48	12.83	12.15
85 (0.2 H_2O)[1]	162-5	65.13	64.87	5.80	5.93	13.21	13.38
86 (0.5 H_2O)[1]	248-51	64.62	64.27	5.42	5.48	13.01	12.92
87 (0.1 H_2O)[1]	261-3	68.41	68.17	6.03	6.03	9.97	10.02
88 (0.1 H_2O)[1]	283-6	66.84	66.52	5.91	6.03	10.62	10.52
89	265-7	65.54	65.13	5.50	5.96	9.97	9.86
90 (0.25 H_2O)[1]	197-9	64.51	64.21	6.14	6.13	8.68	8.64
91 (0.7 H_2O)[1]	213-5	65.75	65.70	6.53	6.18	10.00	10.13
92 (0.25 H_2O)[1]	211-3	65.51	65.71	5.84	5.88	9.55	9.39
93 (0.5 H_2O)[1]	249-53	66.64	66.43	5.84	5.61	10.14	10.03
94 (1 H_2O)[1]	236-8	63.45	63.23	5.83	5.66	10.57	10.48
95 (0.2 H_2O)[1]	253-5	66.54	66.42	5.94	5.82	10.58	10.55
96 (0.25 H_2O)[1]	232-5	64.84	64.72	5.56	5.69	9.86	9.72
97	249-50	68.71	68.35	6.01	6.12	10.01	9.97
98 (0.5 H_2O)[1]	250-4	66.64	66.83	5.84	5.84	10.14	10.04
99 (0.5 H_2O)[1]	266-8	64.93	64.71	5.71	5.61	10.82	10.63

100 (0.25 H_2O)[1]	244-6	67.04	66.67	6.24	6.37	10.20	10.10
101 (0.5 H_2O)[1]	271-2	67.26	67.09	6.11	6.14	9.80	9.76
102 (0.25 H_2O)[1]	250 (d)	67.97	67.58	6.06	6.00	9.91	10.01
103	220 (d)	NA	NA	NA	NA	NA	NA
104 (0.25 H_2O)[1]	244-6	64.64	64.38	6.36	6.64	11.60	11.37
105 (1 H_2O)[1]	230-5	61.44	61.72	5.40	5.07	13.65	13.46
106 (0.8 H_2O)[1]	146-8	61.28	60.99	4.65	4.73	8.57	9.02
107 (0.5 H_2O)[1]	190-4	66.48	66.54	6.55	6.49	13.48	13.27
108	220-4	66.47	66.27	5.58	5.70	11.07	10.90
109	290-4	65.13	64.59	4.03	4.28	7.99	8.18
110	259-60	64.91	64.72	5.67	5.69	12.11	12.01
111	289-91	64.85	64.70	5.19	5.27	10.31	10.34
112	260-1	66.33	66.21	6.03	6.10	12.89	12.71
113	282-5	68.70	68.42	4.88	5.00	12.33	12.39
114	255-65	67.24	67.45	5.87	5.94	12.55	12.40
115 (1 H_2O)[1]	270-2	62.99	62.75	5.98	6.13	12.78	12.90
116 (0.25 H_2O)[1]	246	65.96	65.71	5.65	5.60	12.82	12.70
117	180-2	67.98	67.59	7.55	7.51	12.79	12.70
118 (0.25 H_2O)[1]	256-8	68.95	68.96	6.48	6.51	11.09	11.08
119	197-200	67.50	67.18	6.54	6.60	12.11	11.97
120 (0.1 DMF)[1]	>320	63.96	63.59	3.72	4.00	8.56	8.56
121 (0.5 H_2O)[1]	233-7	64.62	64.85	5.42	5.36	13.10	13.05
122 (0.5 H_2O)[1]	265-8	63.00	62.95	5.51	5.38	12.24	12.07

1) The molecular weight calculated for the elemental analysis includes the solvent in the amount indicated.

III. (7-Azaindol-3-yl)methylene Benzothiazinones (XIII).



XIII.

Example 131: Synthesis of 2-{[1-(4-Acetoxybutyl)-7-azaindol-3-yl]methylene}-2H-1,4-benzothiazine-3(4H)-one:

A mixture of 2-[(1-(4-hydroxybutyl)-7-azaindol-3-yl]methylene-2H-1,4-benzothiazin-3(4H)-one (0.58 g, 1.6 mmol) and acetic anhydride (20 ml) was heated at 100°C for 10 min. After cooling, the reaction mixture was poured into ice water (75 ml) with stirring. The precipitate was collected by filtration and purified by silica gel chromatography using (8 : 2) ethyl acetate : hexane as the mobile phase.

Examples 123-209 from Tables 5-36 were synthesized by the method indicated therein, using an appropriately substituted 2H-1,4-benzothiazin-3(4H)-one and an appropriately substituted 7-azaindole-3-carboxaldehyde, pyrrolo[2,3-c]pyridin-5-carboxaldehyde, imidazole-2-carboxaldehyde, imidazole-5-carboxaldehyde, furan-3-carboxaldehyde, thiophene-3-carboxaldehyde, pyrazole-4-carboxaldehyde, indole-2-carboxaldehyde, pyrrole-3-carboxaldehyde, indazole-3-carboxaldehyde, thiazole-2-carboxaldehyde, pyrazole-3-carboxaldehyde, thiazole-5-carboxaldehyde, indole-4-carboxaldehyde or indole-7-carboxaldehyde.

Methanesulfonic acid salts were formed as described in Example 39 (salt).

Table 5: Compounds synthesized having structural formula XIII.

Example	Substituent on Ring A	Substituent on Ring B	Chromatographic Mobile Phase	% Yield	Method
123	none	1-(4-hydroxy-butyl)	(100 : 1) to (100 : 20) toluene : ethanol	52	see Example 28
124	7-NO_2	none	(100 : 1) to (100 : 20) toluene : ethanol	34	see Example 28
125	7-OH	none	(100 : 1) to (100 : 20) toluene : ethanol	17	see Example 28
126	none	none	(100 : 1) to (100 : 20) toluene : ethanol	56	see Example 28
126 (salt)	none	none	NA	87	see Example 39 (salt)
127	none	1-(2-hydroxy-ethyl-oxymethyl)	(95 : 5) dichloromethane : methanol	19	see Example 28
127 (salt)	none	1-(2-hydroxy-ethyl-oxymethyl)	NA	40	see Example 39 (salt)
128	none	1-(N,N-dimethyl-3-aminopropyl)	(100 : 1) to (100 : 20) toluene : ethanol	49	see Example 28
128 (salt)	none	1-(N,N-dimethyl-3-aminopropyl)	NA	52	see Example 39 (salt)
129	none	1-(2-morpholino ethyl)	(100 : 1) to (100 : 20) toluene : ethanol	26	see Example 28
129 (salt)	none	1-(2-morpholino ethyl)	NA	59	see Example 39 (salt)
130	7-(N,N-dimethyl-3-aminopropyloxy)	none	(100 : 1) to (100 : 20) toluene : ethanol	37	see Example 28
130 (salt)	7-(N,N-dimethyl-3-aminopropyloxy)	none	NA	69	see Example 39 (salt)
131	none	1-(4-acetoxy-butyl)	(8 : 2) ethyl acetate:n-hexane	63	see Example 131

132	none	1-(2-hydroxy ethyl)	(98 : 2) to (7 : 3) CH_2Cl_2:EtOH	29	see example 28
133	none	1-methyl	NA	69	see example 28
134	none	1-methoxy methyl	(98 : 2) to (80 : 20) toluene : ethanol	80	see example 60
135	none	1-(2-dimethyl aminomethyl)	NA	45	see example 60
136	none	1-ethoxycarbonyl methyl	NA	66	see example 17
137	none	1-[N-(2-morpholino ethyl) carbamoyl methyl]	NA	65	see example 24
138	none	1-carboxymethyl	NA	51	*
139	none	1-[N-(3-(4-methyl piperazin-1-yl) propyl) carbamoyl methyl]	NA	50	see example 24
140	none	1-(4-methyl piperazin-1-yl) carbonylmethyl	(9 : 1) to (8 : 2) CH_2Cl_2 : EtOH	45	see example 24
141	none	1-[N-(2-N',N'-diethylamino ethyl)-N-methyl] carbamoyl methyl	(7 : 3) to (0 : 10) ethyl acetate : methanol	19	see example 24
142	none	1-[N-(1-ethylpyrrolidin-2-yl)methyl] carbamoyl methyl	NA	85	see example 79
143	none	1-(4-methylhomopipe razin-1-yl) carbonylmethyl	NA	74	see example 79
144	none	1-(4-ethylpiperazin-1-yl)carbonyl methyl	(95 : 5) to (90 : 10) Cl_2CH_2 : methanol	74	see example 79

145	none	1-(4-piperidinopiperidin-1-yl) carbonylmethyl	(6 : 4) toluene : methanol	81	see example 79
146	none	1-[N,N-bis(2-N',N'-diethyl aminoethyl)carbamoylmethyl]	methanol	19	see example 79

* These compounds were obtained from the corresponding (7-azaindol-3-yl)methylene benzothiazinones already described, by methods well known for those skilled in the art.

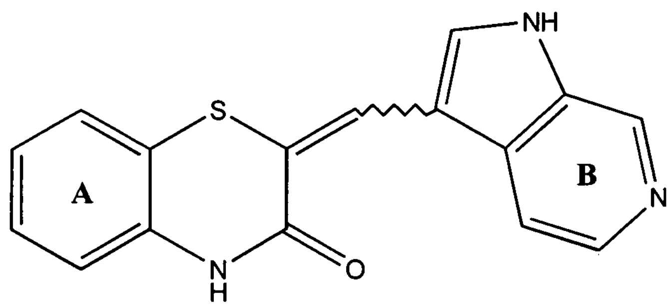
Table 6: Physical data for compounds synthesized having structural formula XIII.

Example	Mp. (°C)	Elemental analysis					
		Carbon		Hydrogen		Nitrogen	
		calculated	found	calculated	found	calculated	found
123	223-4	65.73	65.54	5.24	5.03	11.50	11.34
124	> 340	56.80	56.67	2.98	3.13	16.56	16.45
125	> 340	62.12	61.68	3.58	3.67	13.58	13.23
126 (0.15 H_2O)[1]	> 340	64.86	64.91	4.14	3.85	14.02	14.19
126 (salt)	341-4	52.43	52.20	3.88	3.67	10.79	10.67
127	218-20	NA	NA	NA	NA	NA	NA
127 (salt) (1.0 H_2O)[1]	196-7	49.89	50.29	4.81	4.56	8.72	8.96
128	186-7	NA	NA	NA	NA	NA	NA
128 (salt) (1.0 H_2O)[1]	255-7	46.92	46.59	5.48	5.41	9.52	9.40
129	243-5	NA	NA	NA	NA	NA	NA
129 (salt) (0.5 H_2O)[1]	270-2	53.99	53.60	5.32	5.74	10.95	10.61

130	295-7	NA	NA	NA	NA	NA	NA
130 (salt) (1.0 H_2O)[1]	178-9	45.68	45.95	5.33	5.04	9.26	9.22
131	158-60	64.85	64.84	5.19	5.23	10.31	10.29
132 (0.5 H_2O)[1]	247-9	62.41	62.27	4.66	4.88	12.13	11.87
133	256-8	66.43	66.23	4.26	4.42	13.67	13.48
134	239-41	64.07	64.12	4.48	4.89	12.45	12.01
135	229-30	65.91	65.47	5.53	5.52	15.37	15.23
136	253-5	63.31	63.32	4.52	4.56	11.07	11.13
137	262-5	62.19	61.69	5.44	5.45	15.11	15.00
138 (0.5 H_2O)[1]	296-7	59.99	60.41	3.92	4.00	11.66	11.65
139 (0.2 H_2O)[1]	230-1	63.18	62.96	6.20	6.31	17.00	16.72
140 (0.25 H_2O)[1]	251-3	63.07	62.91	5.41	5.39	15.99	15.53
141 (0.25 H_2O)[1]	152-7	64.15	64.15	6.35	6.41	14.96	14.88
142 (0.2 H_2O)[1]	228-30	64.55	64.54	5.94	6.06	15.05	15.00
143 (0.5 H_2O)[1]	222-4	63.14	63.07	5.74	5.77	15.34	15.08
144 (0.25 toluene)[1]	224-6	65.72	65.86	5.78	6.04	14.88	14.81
145	237-40	67.04	66.61	6.23	6.29	13.96	13.92
146 (0.5 H_2O)[1]	144-54	64.60	64.80	7.41	7.02	15.07	14.79

1) The molecular weight calculated for the elemental analysis includes the solvent in the amount indicated.

IV. (Pyrrolo[2,3-c]pyridin-5-yl)methylene Benzothiazinones (XIV).



XIV.

Table 7: Compounds synthesized having structural formula XIV.

Example	Substituent on Ring A	Substituent on Ring B	Chromatographic Mobile Phase	% Yield	Method
147	none	7-benzyloxy	(100 : 1) to (100 : 20) toluene : ethanol	29	see Example 28
148	none	7-hydroxy	NA	72	*
149	none	1-(2-diethylaminoethyl)-7-hydroxy	(40 : 60) to (30 : 70) Cl_2CH_2 : methanol	45	*

* These compounds were obtained from the corresponding (pyrrolo[2,3-c]pyridin-5-yl)methylenebenzothiazinones already described, by methods well known to those skilled in the art.

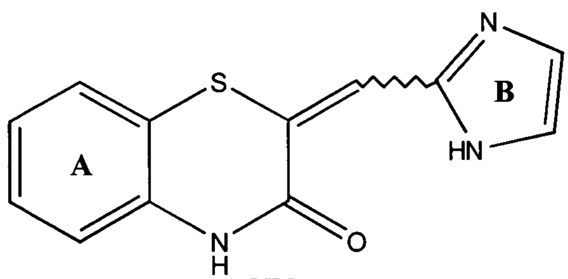
Table 8: Physical data for compounds synthesized having structural formula XIV.

Example	Mp. (°C)	Elemental analysis					
		Carbon		Hydrogen		Nitrogen	
		Calculated	found	calculated	found	calculated	found
147 (0.25 H_2O)[1]	301-2	68.38	68.67	4.36	4.33	10.40	10.53

148 (0.75 H_2O)[1]	>350	59.52	59.58	3.90	4.32	13.01	13.14
149 (0.75 H_2O)[1]	>350	62.61	62.58	6.09	5.79	13.27	13.19

1) The molecular weight calculated for the elemental analysis includes the solvent in the amount indicated.

V. (Imidazol-2-yl)methylene Benzothiazinones (XV).



XV.

Table 9: Compounds synthesized having structural formula XV.

Example	Substituent on Ring A	Substituent on Ring B	Chromatographic Mobile Phase	% Yield	Method
150	None	none	(9 : 1) dichloromethane : ethanol	15	see Example 28
151 (E)-isomer	none	4-trifluoromethyl	(95 : 5) to (97 : 3) dichloromethane : ethyl acetate to dichloromethane : ethanol	20	see Example 17

151 (Z)-isomer	none	4-trifluoromethyl	(95 : 5) to (97 : 3) dichloromethane : ethyl acetate to dichloromethane : ethanol	65	see Example 17
152 (Z)-isomer	none	4-cyano		83	*

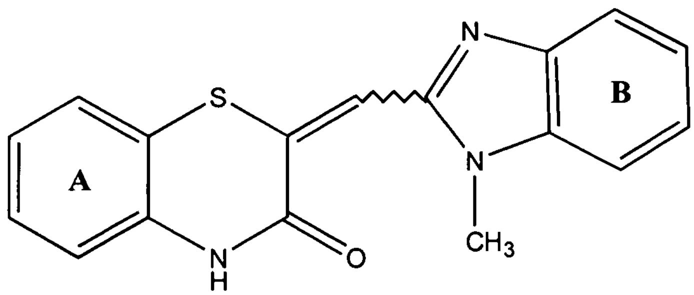
* This compound was obtained from the corresponding (imidazol-2-yl) methylenebenzoxazinone already described, by methods well known to those skilled in the art.

Table 10: Physical data for compounds synthesized having structural formula XV.

Example	Mp. (°C)	Elemental analysis					
		Carbon		Hydrogen		Nitrogen	
		calculated	found	calculated	found	calculated	found
150	321-3	59.24	59.18	3.73	3.82	17.27	16.79
151 (E)-isomer	270-2	50.16	50.43	2.59	2.54	13.50	13.49
151 (E)-isomer (0.8 EtOH)[1]	271-4	50.37	50.59	3.70	3.64	12.07	12.04
152 (Z)-isomer (0.9 EtOH)[1]	>350	57.39	57.10	4.36	4.53	18.08	17.72

1) The molecular weight calculated for the elemental analysis includes the solvent in the amount indicated.

VI. (1-Methyl-1H-benzo[d]imidazol-2-yl)methylene Benzothiazinones (XVI).



XVI.

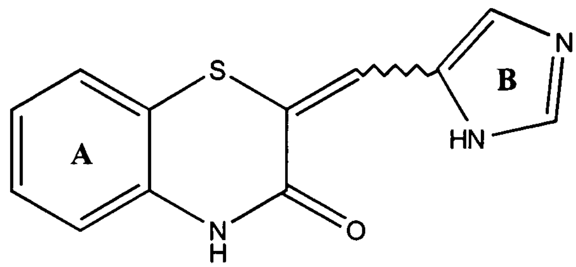
Table 11: Compounds synthesized having structural formula XVI.

Example	Substituent on Ring A	Substituent on 3-azaindole ring	Chromatographic Mobile Phase	% Yield	Method
153	none	1-CH_3	(100:1) to (100:20) Toluene : Ethanol	89	See Example 28

Table 12: Physical data for compounds synthesized having structural formula XVI.

Example	Mp. (°C)	Elemental analysis					
		Carbon		Hydrogen		Nitrogen	
		calculated	found	calculated	found	Calculated	found
153	332-3	66.43	66.40	4.26	4.23	13.67	13.65

VII. (Imidazol-5-yl)methylene Benzothiazinones (XVII).



XVII.

Table 13: Compounds synthesized having structural formula XVII.

Example	Substituent on Ring A	Substituent on Ring B	Chromatographic Mobile Phase	% Yield	Method
154	none	4-CH_3	(98 : 2) to (95 : 5) dichloromethane : ethanol	31	see Example 28
155	none	none	(8 : 2) dichloromethane:methanol	41	see Example 28
156	7-NO_2	4-CH_3	NA	53	see Example 28
157	7-NH_2	4-CH_3	(95:5) dichloromethane:methanol	16	see Example 41
158	none	2-CH_3	(95:5) ethyl acetate:ethanol	26	see Example 28
159	none	2-ethyl-4-methyl	(85:15) to (90:10) ethyl acetate:hexane	44	see Example 28
160	none	3-(2-diethylamino ethyl)-4-CH_3	NA	38	see Example 60
161	none	1-(2-diethylamino ethyl)-4-CH_3	NA	21	see Example 60
162	none	1-(2-morpholinoethyl)-4-CH_3	NA	6	see Example 60
163	none	3-(2-morpholinoethyl)-4-CH_3	NA	30	see Example 60

164 (Z)-isomer	none	1-methyl-2-methylthio	NA	85	see Example 17
165 mixture of Z/E isomers	none	4-methoxy carbonyl	NA	78 as a mixture of isomers	see Example 17
166 (Z)-isomer	none	4-hydroxy methyl	NA	29	see Example 17

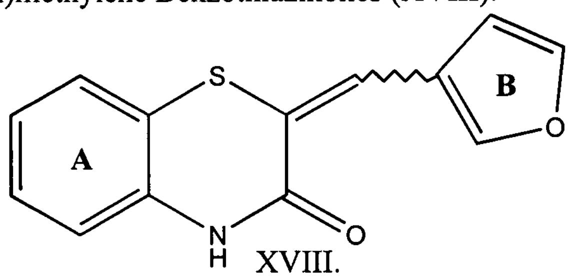
Table 14: Physical data for compounds synthesized having structural formula XVII.

Example	Mp. (°C)	Elemental analysis					
		Carbon		Hydrogen		Nitrogen	
		calculated	found	calculated	found	calculated	found
154	255-7	60.68	60.15	4.31	4.41	16.33	16.10
155	314-5	59.24	59.17	3.73	4.01	17.27	17.35
156 (0.5 H2O)1	325-7	50.16	50.20	3.56	3.82	18.00	18.05
157	281-4	57.34	57.04	4.44	4.65	20.57	20.15
158	282-4	60.68	60.53	4.31	4.15	16.33	16.09
159	280-2	63.13	63.11	5.30	5.46	14.72	14.54
160	198-9	64.01	64.01	6.78	6.81	15.72	15.65
161	150-2	64.01	63.83	6.78	6.77	15.72	15.53
162	245-7	61.60	61.59	5.98	6.04	15.12	14.97
163 (0.2 H_2O)[1]	200-2	61.00	60.85	6.03	5.95	14.97	14.79
164 (Z)-isomer	261-3	55.42	55.61	4.32	4.40	13.85	13.81

165 mixture of Z/E isomers	262-6	55.81	55.83	3.68	3.84	13.95	13.90
166 (Z)-isomer	252-4	57.13	57.24	4.06	4.19	15.37	15.24

1) The molecular weight calculated for the elemental analysis includes the solvent in the amount indicated.

VIII. (Furan-3-yl)methylene Benzothiazinones (XVIII).



XVIII.

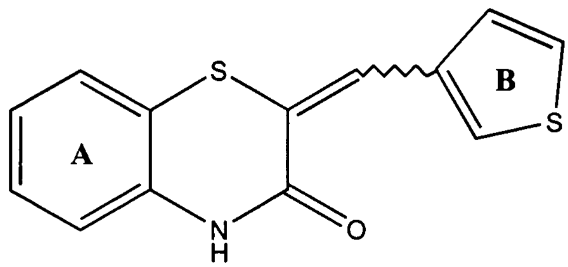
Table 15: Compounds synthesized having structural formula XVIII.

Example	Substituent on Ring A	Substituent on Ring B	Chromatographic Mobile Phase	% Yield	Method
167	none	none	(100 : 1) to (100 : 20) toluene : ethanol	81	see Example 28

Table 16: Physical data for compounds synthesized having structural formula XVIII.

Example	Mp. (°C)	Elemental analysis					
		Carbon		Hydrogen		Nitrogen	
		calculated	found	calculated	found	calculated	found
167	193-5	64.18	64.06	3.73	3.95	5.76	5.74

IX. (Thien-3-yl)methylene Benzothiazinones (XIX).



XIX.

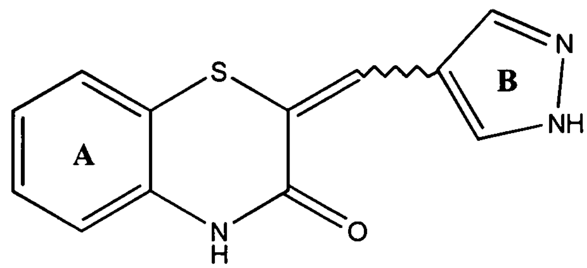
Table 17: Compounds synthesized having structural formula XIX.

Example	Substituent on Ring A	Substituent on Ring B	Chromatographic Mobile Phase	% Yield	Method
168	none	none	(100 : 1) to (100 : 20) toluene : ethanol	93	see Example 28

Table 18: Physical data for compounds synthesized having structural formula XIX.

Example	Mp. (°C)	Elemental analysis					
		Carbon		Hydrogen		Nitrogen	
		calculated	found	calculated	found	calculated	found
168	229-31	60.21	60.07	3.49	3.72	5.40	5.40

X. (Pyrazol-4-yl)methylene Benzothiazinones (XX).



XX.

Table 19: Compounds synthesized having structural formula XX.

Example	Substituent on Ring A	Substituent on Ring B	Chromatographic Mobile Phase	% Yield	Method
169	none	3-CH_3	(100 : 1) to (100 : 20) toluene : ethanol	69	see Example 28
170	none	3-Phenyl	NA	89	see Example 28
171	none	1-(2-diethyl aminoethyl)-3-methyl	NA	24	see Example 60
172	none	1-(2-diethyl aminoethyl)-5-methyl	NA	19	see Example 60
173	none	1-(2-morpholinoethyl)-3-methyl	(90 : 10) ethyl acetate : ethanol	24	see Example 60
174	none	1-(morpholinethyl)-5-methyl	(90 : 10) ethyl acetate : ethanol	33	see Example 60
175	none	1-CH_3	NA	86	see Example 17
176	none	1-$C(CH_3)_3$	NA	83	see Example 17
177	none	1-ethoxy carbonyl methyl-3-methyl	(100 : 0) to (95 : 5) CH_2Cl_2 : CH_3OH	66 as a mixture of isomers	see Example 17

178	none	1-ethoxy carbonyl methyl-5-methyl	(100 : 0) to (95 : 5) $CH_2Cl_2 : CH_3OH$	66 as a mixture of isomers	see Example 17
179	none	1-carboxy methyl-3-methyl	NA	100	*
180	none	1-carboxy methyl-5-methyl	NA	97	*
181	none	1-[N-(2-dimethyl aminoethyl) carbamoyl methyl]-3-methyl	NA	65	see Example 24
182	none	1-[N-(3-(4-methyl piperazin-1-yl)propyl) carbamoyl methyl]-3-methyl	NA	85	see Example 24
183	none	1-[N-(2-dimethyl aminoethyl) carbamoyl methyl]-5-methyl	NA	59	see Example 24
184	none	1-[N-(2-morpholinoet hyl)carbamoyl methyl]-3-methyl	NA	79	see Example 24
185	none	1-[(4-piperidino piperidin-1-yl)carbonyl methyl]-3-methyl	NA	86	see Example 79

186	none	1-[N-(2-N',N'-diethyl aminoethyl)-N-methyl] carbamoyl methyl-3-methyl	(4 : 6) CH_2Cl_2 : MeOH	78	see Example 79
187	none	1-(4-methyl piperazin-1-yl)carbonyl methyl-5-methyl	NA	28	see Example 79
188	none	1-(4-methyl piperazin-1-yl)carbonyl methyl-3-methyl	NA	45	see Example 79
189	none	1-[N-(3-(imidazol-1-yl)propyl) carbamoyl methyl]-3-methyl	NA	90	see Example 79
190	none	1-[4-(2-hydroxyethyl) piperazin-1-yl]carbonyl methyl-5-methyl	NA	95	see Example 79
191	none	1-{4-[2-(2-hydroxy ethoxy)ethyl] piperazin-1-yl}carbonyl methyl-5-methyl	(9 : 1) CH_2Cl_2 : MeOH	59	see Example 79

* These compounds were obtained from the corresponding (pyrazol-4-yl) methylene benzothiazinones already described, by methods well known to those skilled in the art.

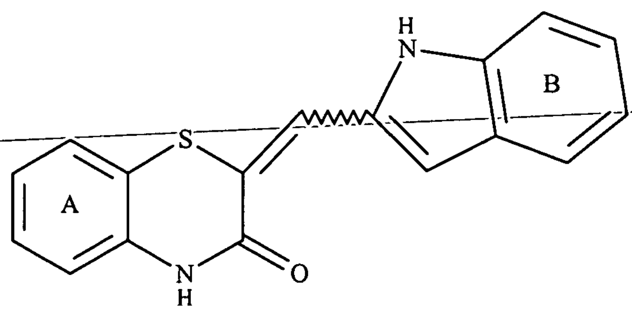
Table 20: Physical data for compounds synthesized having structural formula XX.

Example	Mp. (°C)	Elemental analysis					
		Carbon		Hydrogen		Nitrogen	
		calculated	found	calculated	found	calculated	found
169	297-9	60.68	60.71	4.31	4.28	16.33	16.41
170	290-2	67.69	67.44	4.10	4.08	13.16	13.06
171 ($0.25\ H_2O$)[1]	160-2	63.21	63.09	6.84	6.95	15.52	15.27
172 ($0.25\ H_2O$)[1]	197-200	63.21	63.56	6.84	6.85	15.52	15.58
173 ($0.25\ H_2O$)[1]	190-1	60.86	61.12	6.05	6.04	14.94	14.99
174	195-6	61.59	61.24	5.98	6.03	15.12	14.96
175	255-6	60.68	60.83	4.31	4.53	16.33	16.29
176	228-30	64.19	64.30	5.72	5.32	14.03	14.07
177	226-7	59.46	59.63	4.99	4.94	12.24	12.20
178	231	59.46	59.47	4.99	4.94	12.24	12.16
179 (0.5 EtOH)[1]	278-82	56.79	56.62	4.77	5.06	12.42	11.85
180	288-92	57.13	57.49	4.16	4.34	13.32	13.26
181	253-5	59.20	58.86	6.01	5.86	18.17	17.85
182 ($0.2\ H_2O$)[1]	250-2	60.29	60.11	6.69	6.53	18.34	18.20
183 ($0.2\ H_2O$)[1]	220-2	58.65	58.56	6.06	5.97	18.00	17.86
184	244-5	59.00	58.84	5.89	5.95	16.38	16.45

185 (0.25 H_2O)[1]	244-8	63.87	63.74	6.75	6.67	14.90	14.74
186	160-70	61.80	61.60	6.84	6.82	16.38	16.17
187 (0.2 H_2O)[1]	285-7	59.89	59.89	5.88	5.97	17.46	17.13
188	263-5	60.43	60.45	5.83	6.02	17.62	17.54
189	228-30	59.70	59.68	5.25	5.35	19.89	20.01
190 (0.25 EtOH)[1]	267-70	58.82	58.65	6.08	5.88	15.95	15.78
191 (1.25 H_2O)[1]	193-5	55.91	55.81	6.43	6.14	14.17	14.06

1) The molecular weight calculated for the elemental analysis includes the solvent in the amount indicated.

XI. (Indol-2-yl)methylene Benzothiazinones (XXI).



XXI.

Table 21. Compounds synthesized having structural formula XXI.

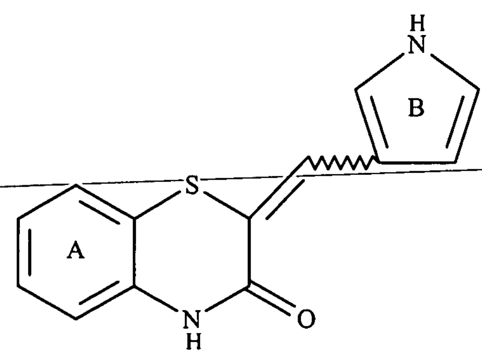
Example	Substituent on Ring A	Substituent on Ring B	Chromatographic Mobile Phase	% Yield	Method
192 (E-isomer)	none	none	(95:5) to (80:20) toluene-ethyl acetate	<10	see Example 28
192 (Z-isomer)	none	none	(95:5) to (80:20) toluene:ethyl acetate	<10	see Example 28

Table 22. Physical data for compounds synthesized having structural formula XXI.

Example	Mp. (°C)	Elemental analysis					
		Carbon		Hydrogen		Nitrogen	
		calculated	found	calculated	found	calculated	found
192 (E-isomer)	270-2	69.84	69.81	4.14	4.32	9.58	9.24
192 (Z-isomer) (0.1 H_2O)[1]	303-5	69.41	69.26	4.18	4.22	9.52	9.19

1) The molecular weight calculated for the elemental analysis includes the solvent in the amount indicated.

XII. (Pyrrol-3-yl)methylene Benzothiazinones (XXII).



XXII.

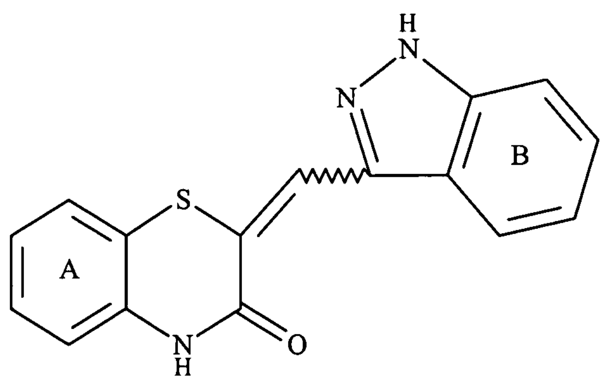
Table 23.Compounds synthesized having structural formula XXII.

Example	Substituent on Ring A	Substituent on Ring B	Chromatographic Mobile Phase	% Yield	Method
193	none	none	(98:2) to (95:5) toluene:ethanol	65	see Example 28

Table 24. Physical data for compounds synthesized having structural formula XXII.

Example	Mp. (°C)	Elemental analysis					
		Carbon		Hydrogen		Nitrogen	
		calculated	found	calculated	found	calculated	found
193	260-2	64.44	64.19	4.16	4.26	11.56	11.21

XIII. (Indazol-3-yl)methylene Benzothiazinones (XXIII).



XXIII.

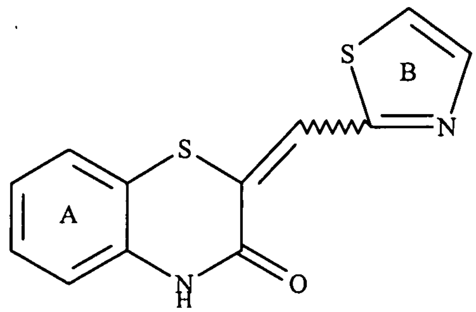
Table 25. Compounds synthesized having structural formula XXIII.

Example	Substituent on Ring A	Substituent on Ring B	Chromatographic Mobile Phase	% Yield	Method
194	none	none	NA	65	see Example 28

Table 26. Physical data for compounds synthesized having structural formula XXIII.

Example	Mp. (°C)	Elemental analysis					
		Carbon		Hydrogen		Nitrogen	
		calculated	found	calculated	found	calculated	found
194	343-5	65.51	65.21	3.78	4.15	14.32	14.42

XIV. (Thiazol-2-yl)methylene Benzothiazinones (XXIV).



XXIV.

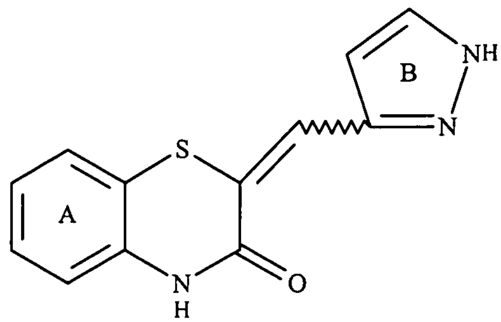
Table 27. Compounds synthesized having structural formula XXIV.

Example	Substituent on Ring A	Substituent on Ring B	Chromatographic Mobile Phase	% Yield	Method
195	None	none	(100:1) CH_2Cl_2:ethanol	13	see Example 28

Table 28. Physical data for compounds synthesized having structural formula XXIV.

Example	Mp. (°C)	Elemental analysis					
		Carbon		Hydrogen		Nitrogen	
		calculated	found	calculated	found	calculated	found
195	272-4	55.36	55.31	3.10	3.22	10.76	10.69

XV. (Pyrazol-3-yl)methylene Benzothiazinones (XXV).



XXV.

Example 196: Synthesis of 2-[(1H-pyrazol-3-yl)methylene]-2H-1,4-benzothiazin-3(4H)-one:

A solution of sodium methoxide (30 mg, 0.55 mmol) in anhydrous methanol (3 ml) was added to a stirred mixture of 2-diethylphosphonyl-2H-1,4-benzothiazin-3(4H)-one (150 mg, 0.5 mmol) and 1H-pyrazole-3-carboxaldehyde (50 mg, 0.5 mmol) in anhydrous methanol (20 ml). Stirring was continued for 19 hours at room temperature, then the precipitated solid was filtered off and washed with methanol.

Table 29. Compounds synthesized having structural formula XXV.

Example	Substituent on Ring A	Substituent on Ring B	Chromatographic Mobile Phase	% Yield	Method
196	None	none	NA	67	see Example 196
197	None	5-ethoxy carbonyl	NA	86	see Example 196
198	None	5-[N-(2-morpholino ethyl)carbamoyl]	NA	76	see Example 24
199	None	5-[N-(2-methoxyethyl) carbamoyl]	NA	82	see Example 24
200	None	5-[N-(2-(pyrrolidin-1-yl) ethyl) carbamoyl]	NA	47	see Example 24

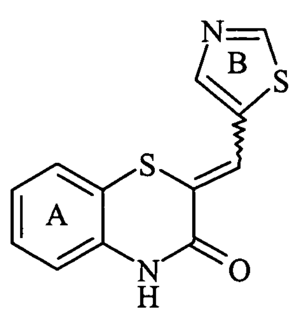
201	None	5-[N-(3-dimethyl aminopropyl) carbamoyl]	NA	69	see Example 24

Table 30. Physical data for compounds synthesized having structural formula XXV.

Example	Mp. (°C)	Elemental analysis					
		Carbon		Hydrogen		Nitrogen	
		calculated	found	calculated	found	calculated	found
196	284-7	59.24	58.69	3.73	3.80	17.27	17.03
197 $(0.7\ H_2O)$[1]	260-2	54.94	54.96	4.43	4.55	12.81	12.73
198	284-6	57.13	57.44	5.30	5.37	17.53	17.42
199	276-80	55.80	56.26	4.68	4.82	16.27	16.28
200	273-5	59.51	59.40	5.52	5.64	18.26	18.20
201 $(0.5\ H_2O)$[1]	265	56.82	56.93	5.83	5.98	18.41	18.03

1) The molecular weight calculated for the elemental analysis includes the solvent in the amount indicated.

XVI. (Thiazol-5-yl)methylene Benzothiazinones (XXVI).



XXVI.

Table 31. Compounds synthesized having structural formula XXVI.

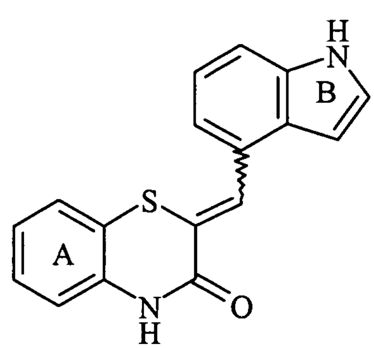
Example	Substituent on Ring A	Substituent on Ring B	Chromatographic Mobile Phase	% Yield	Method
202	none	2-dimethyl amino	NA	83	see Example 196

Table 32. Physical data for compounds synthesized having structural formula XXVI.

Example	Mp. (°C)	Elemental analysis					
		Carbon		Hydrogen		Nitrogen	
		calculated	found	calculated	found	calculated	found
202 (0.5 EtOH)[1]	258-60	55.19	55.33	4.94	4.88	12.87	12.92

1) The molecular weight calculated for the elemental analysis includes the solvent in the amount indicated.

XVII. (Indol-4-yl)methylene Benzothiazinones (XXVII).



XXVII

Table 33. Compounds synthesized having structural formula XXVII.

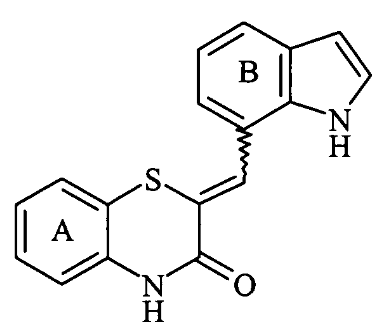
Example	Substituent on Ring A	Substituent on Ring B	Chromatographic Mobile Phase	% Yield	Method
203	none	none	NA	48 as a mixture of Z/E isomers	see Example 17
204	none	3-morpholinomethyl	(100 : 1) to (100 : 4) CH_2Cl_2 : EtOH	43 as a mixture of Z/E isomers	see Example 17

Table 34. Physical data for compounds synthesized having structural formula XXVII.

Example	Mp. (°C)	Elemental analysis					
		Carbon		Hydrogen		Nitrogen	
		calculated	found	calculated	found	calculated	found
203	218-20	69.84	69.48	4.14	4.26	9.48	9.58
204 $(0.25 H_2O)^1$	137-40	66.73	66.66	5.47	5.58	10.61	10.56

1) The molecular weight calculated for the elemental analysis includes the solvent in the amount indicated.

XVIII. (Indol-7-yl)methylene Benzothiazinones (XXVIII).



XXVIII

Table 35. Compounds synthesized having structural formula XXVIII.

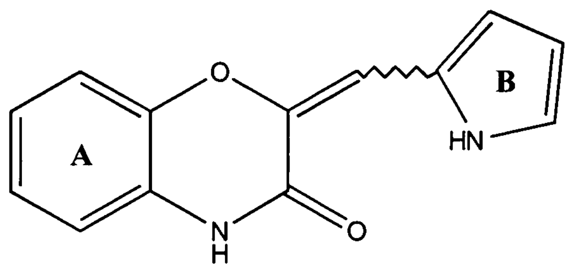
Example	Substituent on Ring A	Substituent on Ring B	Chromatographic Mobile Phase	% Yield	Method
205	none	none	NA	64	see Example 17
206	none	3-(dimethyl amino)methyl	NA	79	see Example 17
207	none	3-morpholinomethyl	NA	90	see Example 17
208	none	3-piperidino methyl	NA	85	see Example 17
209	none	3-(4-methyl piperazin-1-yl)methyl	NA	74	see Example 17

Table 36. Physical data for compounds synthesized having structural formula XXVIII.

Example	Mp. (°C)	Elemental analysis					
		Carbon		Hydrogen		Nitrogen	
		calculated	found	calculated	found	calculated	found
205	235-7	69.84	69.73	4.14	4.27	9.58	9.48
206 (0.1 toluene)[1]	185-92	69.32	69.44	5.56	5.66	11.72	11.82
207	219-24	67.50	67.50	5.41	5.57	10.73	10.72
208 (0.5 CH_3OH)[1]	110-15	69.60	69.28	6.21	6.19	10.36	10.22
209 (0.1 AcOEt)[1]	220-4	68.00	68.07	6.05	6.25	13.55	13.30

1) The molecular weight calculated for the elemental analysis includes the solvent in the amount indicated.

XIX. (Pyrrol-2-yl)methylene Benzoxazinones (XXIX).



XXIX.

Example 210: Synthesis of 2-[(Pyrrol-2-yl)methylene]-2H-1,4-benzoxazin-3(4H)-one:

Sodium methoxide (0.65 g, 0.012 mol) was added in one portion to a mixture of 2H-1,4-benzoxazin-3(4H)-one (1.49 g, 0,01 mol) and pyrrole-2-carboxaldehyde (1.58 g, 0.016 mol) in dry DMF (10 ml). The reaction mixture was refluxed for 48 h, then cooled at room temperature and poured into crushed ice and left overnight at 4°C. The precipitated solid was collected by filtration, washed with water and dried. The precipitate was boiled with ethanol (150 ml) and filtered while hot to remove impurities. The filtrate was evaporated to dryness under reduced pressure, and the residue was chromatographed on a silica gel column using (95 : 5) toluene : ethyl acetate as the mobile phase.

Example 221: Synthesis of (Z) and (E)-2-[(1-Methylpyrrol-2-yl)methylene]-2H-1,4-benzoxazin-3(4H)-one:

Sodium methoxide (0.15 g, 0.0027 mol) was added in one portion to a mixture of 2-diethylphosphonyl-2H-1,4-benzoxazin-3(4H)-one (0.57 g, 0.002 mol) and 1-methylpyrrole-2-carboxaldehyde (0.22 g, 0.002 mol) in methanol (20 ml). The reaction mixture was stirred at room temperature for 48 h. The precipitated solid was collected by filtration and washed with cold methanol to give the corresponding (E)-isomer. The filtrate was evaporated to dryness, and the residue was chromatographed on a silica gel

column using (97 : 3) dichloromethane : ethanol as the mobile phase to give the corresponding (Z)-isomer.

Table 37 lists the compounds that were synthesized having structural formula XXIX. Examples 210-220 in table 37 were synthesized as described in Example 210 using an appropriately substituted 2H-1,4-benzoxazin-3(4H)-one and an appropriately pyrrole-2-carboxaldehyde. Examples 221-222 in table 37 were synthesized as described in example 221 using an appropriately substituted 2H-1,4-benzoxazin-3(4H) and an appropriately pyrrole-2-carboxaldehyde.

Table 37: Compounds synthesized having structural formula XXIX.

Example	Substituent on Ring A	Substituent on Ring B	Chromatographic Mobile Phase	% Yield (E)-isomer	% Yield (Z)-isomer	Method
210	none	none	(95 : 5) toluene : ethyl acetate	3	20	see Example 210
211	6-Cl	none	(95 : 5) toluene : ethyl acetate	2	22	see Example 210
212	6-CH_3	none	(95 : 5) toluene : ethyl acetate	2	17	see Example 210
213	7-CH_3	none	(95 : 5) toluene : ethyl acetate	2	19	see Example 210
214	6-OCH_3	none	(95 : 5) toluene : ethyl acetate	1	13	see Example 210
215	7-Cl	none	(95 : 5) toluene : ethyl acetate	2	23	see Example 210
216	7-OCH_3	none	(95 : 5) toluene : ethyl acetate	1	19	see Example 210
217	6-CN	none	(95 : 5) toluene : ethyl acetate	0	15	see Example 210
218	5-CH_3	none	(95 : 5) toluene : ethyl acetate	1	19	see Example 210

219	6,7-Cl	none	(95 : 5) toluene : ethyl acetate	1	20	see Example 210
220	none	5-CH_3	(90 : 10) toluene:ethylacetate	0	9	see Example 210
221	none	1-methyl	(97 : 3) dichloromethane : ethanol	57	23	see Example 221
222	none	3,5-dimethyl	toluene to (90 : 10) toluene : ethanol	39	34	see Example 221
223 salt	none	3,5-dimethyl-4-amino methyl	NA	43	-	*
224	none	3,5-dimethyl-4-amino methyl	NA	-	74	*

* These compounds were obtained from the corresponding (pirrol-2-yl) methylene benzoxazinones already described by methods well known to those skilled in the art. Example 223 is hydroiodide.

Table 38: Physical data for compounds synthesized having structural formula XXIX.

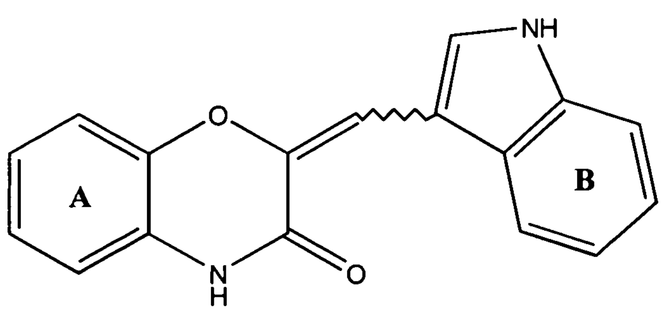
Example	Mp. (°C)	Elemental analysis					
		Carbon		Hydrogen		Nitrogen	
		calculated	found	calculated	found	calculated	found
210 (E)-isomer	233-5	69.02	69.04	4.46	4.45	12.38	12.18
210 (Z)-isomer	263-5	69.02	68.91	4.46	4.59	12.38	12.21
211 (E)-isomer	259-61	59.90	59.40	3.48	3.52	10.75	10.53

211 (Z)-isomer	284-6	59.90	59.89	3.48	3.59	10.75	10.54
212 (E)-isomer	243-6	69.99	69.70	5.03	5.28	11.66	11.62
212 (Z)-isomer	299-300	69.99	69.86	5.03	5.09	11.66	11.52
213 (E)-isomer	205-8	69.99	69.76	5.03	5.01	11.66	11.56
213 (Z)-isomer (0.25 H_2O)[1]	250-2	68.64	68.91	5.10	4.80	11.46	11.32
214 (E)-isomer	230-2	65.62	65.38	4.72	4.96	10.93	10.80
214 (Z)-isomer	250-1	65.62	65.48	4.72	4.54	10.93	10.86
215 (E)-isomer	240-2	59.90	60.03	3.48	3.71	10.75	10.67
215 (Z)-isomer	278-80	59.90	60.11	3.48	3.70	10.75	10.51
216 (E)-isomer	214-7	65.62	65.51	4.72	4.91	10.93	10.82
216 (Z)-isomer	276-8	65.62	65.61	4.72	4.74	10.93	10.92
217 (Z)-isomer	285-7	66.93	66.61	3.61	3.90	16.72	16.53
218 (E)-isomer	220-2	69.99	69.75	5.03	5.10	11.66	11.58
218 (Z)-isomer	256-8	69.99	70.13	5.03	5.24	11.66	11.88
219 (E)-isomer	272-4	52.91	53.04	2.73	2.81	9.49	9.43

219 (Z)-isomer	323-5	64.72	64.48	4.59	4.66	17.41	17.20
220 (Z)-isomer	248-50	69.99	69.81	5.03	5.09	11.66	11.36
221 (E)-isomer	218-20	69.76	69.99	4.94	5.03	11.57	11.66
221 (Z)-isomer	263-5	59.76	69.30	4.94	5.23	11.57	11.41
222 (E)-isomer (0.2 H_2O)[1]	224-6	69-86	69.56	5.63	5.65	10.86	10.69
222 (Z)-isomer (0.2 C_2H_5OH)[1]	248-50	70.19	70.02	5.81	5.57	10.63	10.69
223 salt (E)-isomer	223-5	49.21	49.41	5.05	5.02	9.56	9.99
224 (Z)-isomer (0.3 H_2O)[1]	234-6	68.24	67.85	6.87	6.80	13.26	12.99

1) The molecular weight calculated for the elemental analysis includes the solvent in the amount indicated.

XX. (Indol-3-yl)methylene Benzoxazinones (XXX).



XXX.

Example 225: Synthesis of 2-[(Indol-3-yl)methylene]-2H-1,4-benzoxazin-3(4H)-one:

Sodium methoxide (0.65 g, 0.012 mol) was added in one portion to a mixture of 2H-1,4-benzoxazin-3(4H)-one (1.49 g, 0.01 mol) and indole-3-carboxaldehyde (2.32 g, 0.016 mol) in dry DMF (10 ml). The reaction mixture was refluxed for 24 h, then cooled at room temperature and poured into crushed ice and left overnight in the refrigerator. The precipitated solid was collected by filtration, washed with water and dried. The crude product was chromatographed on silica gel using (9 : 1) toluene : ethyl acetate.

Example 231: Synthesis of 2-[(6-Methoxycarbonylindol-3-yl)methylene]-2H-1,4-benzoxazin-3(4H)-one:

Sodium methoxide (1 g, 0.018 mol) was added in one portion to a mixture of 2-diethylphosphonyl-2H-1,4-benzoxazin-3(4H)-one (3.42 g, 0.012 mol) and 6-methoxycarbonylindol-3-carboxaldehyde (2.55 g, 0.012 mol) in methanol (60 ml). The reaction mixture was refluxed for 21 h, then cooled at room temperature and the precipitated solid was collected by filtration, washed with methanol and dried. Yield 2.78 g (87%) as a mixture of isomers.

Example 232: Synthesis of (Z)-2-[(6-carboxyindol-3-yl)methylene]-2H-1,4-benzoxazin-3(4H)-one:

2-[(6-Methoxycarbonylindol-3-yl)methylene]-2H-1,4-benzoxazin-3(4H)-one (2.16 g, 0.008 mol) was heated at reflux in an aqueous sodium hydroxyde solution (6.5 g in 110 ml) for 2 h. The solution was cooled and acidified with concentrate HCl. The precipitated solid was filtered, washed with water and dried to yield 1.8 g, (69%) as (Z)-isomer.

Example 233: Synthesis of (Z)-2-{[6-(N,N-dimethyl-3-aminopropylcarbamoyl)indol-3-yl]methylene}-2H-1,4-benzoxazin-3(4H)-one:

Carbonyldiimidazole (0.6 g, 0.0037 mol) was added in one portion under nitrogen atmosphere to a solution of (Z)-2-{[6-carboxyindol-3-yl)methylene]-2H-1,4-benzoxazin-3(4H)-one (0.9 g, 0.0028 mol) in dry N,N-dimethylformamide (45 ml). The reaction mixture was heated at 40°C for 2 h. The N,N-dimethyl-3-aminopropylamine (0.92 g, 0.009 mol) was added and the mixture was heated at 40°C for 20 hr. The solvent was evaporated to dryness under reduced pressure and the residue was stirred with dichloromethane. The precipitated solid was collected by filtration, washed with cichloromethane and dried. The crude product was purified by recrystallization from N,N-dimethylformamide : water.

Examples 225-230 Table 39 were synthesized as described in Example 225 using an appropriately substituted 2H-1,4-benzoxazin-3(4H)-one and an appropriately substituted indole-3-carboxaldehyde. Examples 231-233 were synthesized as described above. Example 234 in Table 39 was synthesized as described in Example 221 using an appropriately substituted 2H-1,4-benzoxazin-3(4H)-one and an appropriately substituted indole-3-carboxaldehyde.

Table 39: Compounds synthesized having structural formula XXX.

Example	Substituent on Ring A	Substituent on Ring B	Chromatographic Mobile Phase	% Yield	Method
225	none	none	(9 : 1) toluene : ethyl acetate	24	see Example 225
226	none	1-(4-hydroxy-butyl)	(9 : 1) toluene : ethyl acetate	21	see Example 225
227	6-CH_3	none	(9 : 1) toluene : ethyl acetate	19	see Example 225
228	6-Cl	none	(9 : 1) toluene : ethyl acetate	18	see Example 225

229	7-CH_3	none	(9 : 1) toluene : ethyl acetate	15	see Example 225
230	5-CH_3	none	(9 : 1) toluene : ethyl acetate	20	see Example 225
231	none	6-methoxy carbonyl	NA	87 as mixture of isomers	see Example 231
232 (Z)-isomer	none	6-carboxy	NA	69	see Example 232
233 (Z)-isomer	none	6-(N,N-dimethyl-3-aminopropyl carbamoyl	NA	90	see Example 233
234 (Z)-isomer	none	6-N,N-dimethyl aminosulfonyl	(8: 2) Dichloromethane : ethylacetate	15	see Example 221
234 (E)-isomer	none	6-N,N-dimethyla minosulfonyl	(8 : 2) dichloromethane : ethylacetate	55	see Example 221

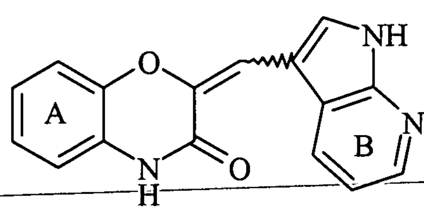
Table 40: Physical data for compounds synthesized having structural formula XXX.

Example	Mp. (°C)	Elemental analysis					
		Carbon		Hydrogen		Nitrogen	
		calculated	found	calculated	found	calculated	found
225	> 300	73.90	73.42	4.38	4.74	10.14	9.91
226	222-5	71.47	70.96	5.85	6.20	7.94	7.45
227 (0.1 H_2O)[1]	235-7	74.01	73.61	4.89	4.90	9.59	9.29
228	315-8	65.71	65.33	3.57	3.61	9.02	8.96
229	309-12	74.47	74.50	4.86	4.92	9.65	9.46
230	310-12	74.47	74.15	4.86	5.03	9.65	9.70

231 (Z)-isomer	215-20	NA	NA	NA	NA	NA	NA
232 (Z)-isomer	>350	NA	NA	NA	NA	NA	NA
233 (0.3 H_2O)[1]	250-3	67.40	67.38	6.05	6.23	13.67	13.56
234 (Z)-isomer	315-7	59.52	59.41	4.47	4.63	10.96	10.73
234 (E)-isomer	248-50	59.52	59.58	4.47	4.58	10.96	10.87

1) The molecular weight calculated for the elemental analysis includes the solvent in the amount indicated.

XXI. (7-Azaindol-3-yl)methylene Benzoxazinones (XXXI).



XXXI

Example 235 was synthesized as described in Example 221 using an appropriately substituted 2H-1,4-benzoxazin-3(4H)-one and an appropriately substituted 7-azaindole-3-carboxaldehyde.

Table 41: Compound synthesized having structural formula XXXI.

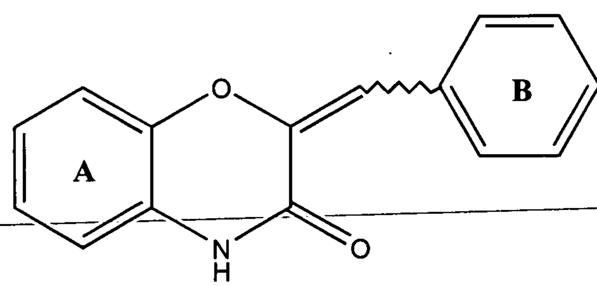
Example	Substituent on Ring A	Substituent on Ring B	Chromatographic Mobile Phase	% Yield	Method
235	none	none	ethanol	65 as a mixture of isomers	see Example 221

Table 42: Physical data for compounds synthesized having structural formula XXXI.

Example	Mp. (°C)	Elemental analysis					
		Carbon		Hydrogen		Nitrogen	
		calculated	found	calculated	found	calculated	found
235 (0.2 C_2H_5OH)[1]	>350	68.75	68.44	4.29	4.19	14.67	14.87

1) The molecular weight calculated for the elemental analysis includes the solvent in the amount indicated.

XXII. (Phenyl)methylene Benzoxazinones (XXXII).



XXXII.

Example 236: Synthesis of 2-[(4-Cyanophenyl)methylene]-2H-1,4-benzoxazin-3(4H)-one:

4-Cyanobenzaldehyde (1.98 g, 0.015 mol) was added to a mixture of 2H-1,4-benzoxazin-3(4H)-one (1.49 g, 0.01 mol), acetic anhydride (4 ml) and triethylamine (2 ml). The reaction mixture was refluxed for 7 h, left overnight at room temperature and poured into crushed ice. The precipitated solid was collected by filtration and washed with acetonitrile. The crude product was purified by recrystalization from DMF : ethanol.

Example 237: Synthesis of 2-[(4-Dimethylaminophenyl)methylene]-2H-1,4-benzoxazin-3(4H)-one:

Sodium methoxide (0.65 g, 0.012 mol) was added in one portion to a mixture of 2H-1,4-benzoxazin-3(4H)-one (1.49 g, 0.01 mol) and 4-dimethylamino benzaldehyde (2.38 g, 0.016 mol) in dry DMF (10 ml). The reaction mixture was refluxed overnight, then cooled to room temperature and poured into crushed ice. The precipitated solid was collected by filtration, washed with water and dried. The crude product was purified by recrystallization from ethanol.

Example 241: Synthesis of 2-[(4-Aminophenyl)methylene]-2H-1,4-benzoxazin-3(4H)-one:

A catalytic amount of Raney nickel was added portionwise with stirring to a mixture of 2-[(4-nitrophenyl)methylene]-2H-1,4-benzoxazin-3(4H)-one (0.57 g, 0.002 mol) and hydrazine hydrate (1 ml) in ethanol (20 ml). The reaction mixture was refluxed for 3 h, then filtered. The filtrate was evaporated to dryness under reduced pressure. The crude product was purified by re crystallization from ethanol.

Example 242: Synthesis of 2-[(4-Hydroxyphenyl)methylene]-2H-1,4-benzoxazin-3(4H)-one:

A mixture of 2-[(4-acetoxyphenyl)methylene]-2H-1,4-benzoxazin-3(4H)-one (0.49 g, 0.0016 mol) and NaOH 10% (30 ml) was refluxed for 1 h. The reaction mixture was cooled and acidified with 6N HCl. The precipitated was collected by filtration, then washed with water and dried. The crude product was purified by recrystalization from ethanol.

Example 245. 2-[(4-Oxamidinophenyl)methylene]-2H-1,4-benzoxazin-3(4H)-one

A mixture of hydroxylamine hydrochloride (145 mg, 2 mmol), sodium carbonate (106 mg, 1 mmol), 2-[(4-cyanophenyl)methylene]-2H-1,4-benzoxazin-3(4H)-one (262

mg, 1 mmol in ethanol (25 ml) and water (3 ml) was refluxed for 25 h. The precipitated solid was filtered off and recristallized from ethanol to give 180 mg (61%).

Table 43 lists the compounds synthesized having structural formula XXXII. Examples 236, 241, 242 and 245 were synthesized as described above. Examples 237-240 were synthesized as described in Example 237. Examples 243 and 244 were synthesized as described in Example 241, and Example 246 was synthesized as described in Example 236 using an appropriately substituted 2H-1,4-benzoxazin-3(4H)-one and an appropriately substituted benzaldehyde.

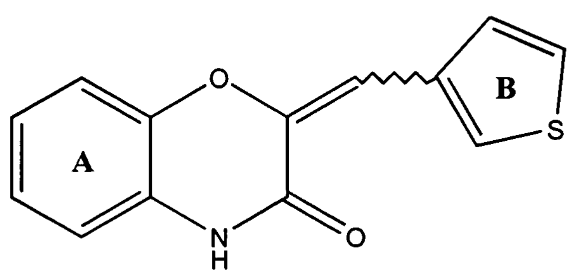
Table 43: Compounds synthesized having structural formula XXXII.

Example	Substituent on Ring A	Substituent on Ring B	Recrystalization Solvent	% Yield	Method
236	none	4-CN	DMF-ethanol	37	see Example 236
237	none	4-$N(CH_3)_2$	ethanol	30	see Example 237
238	6-Cl	4-$N(CH_3)_2$	DMF – ethanol	40	see Example 237
239	6-CH_3	4-$N(CH_3)_2$	DMF – ethanol	45	see Example 237
240	7-CH_3	4-$N(CH_3)_2$	acetonitrile	35	see Example 237
241	none	4-NH_2	ethanol	64	see Example 241
242	none	4-OH	NA	97	see Example 242
243	6-NH_2	4- NH_2	ethanol	74	see Example 241
244	7- NH_2	4- NH_2	ethanol-hexane	20	see Example 241
245	none	4-$C(=NOH)NH_2$	ethanol	61	see Example 245
246	none	3,4-$(OCOCH_3)_2$	ethylacetate	10	see Example 236

Table 44: Physical data for compounds synthesized having structural formula XXXII.

Example	Mp. (°C)	Elemental analysis					
		Carbon		Hydrogen		Nitrogen	
		calculated	found	calculated	found	calculated	found
236	330-2	73.27	73.20	3.84	4.09	10.68	10.61
237	245-7	72.84	72.83	5.75	5.78	9.99	9.89
238	307-9	64.87	64.71	4.80	4.69	8.90	9.17
239	290-2	73.45	73.24	6.16	6.21	9.52	9.51
240	240-3	72.56	72.51	6.22	6.20	9.40	9.37
241	297-299	71.42	71.30	4.79	4.84	11.10	11.02
242	275-7	70.47	70.19	4.68	4.78	5.34	5.28
243	285-7	67.41	67.07	4.90	5.07	15.72	15.56
244	277-9	65.76	65.12	5.78	5.52	14.03	14.59
245	276-8	65.08	65.18	4.44	4.71	14.23	13.87
246	223-5	64.59	64.50	4.28	4.53	3.96	3.86

XXIII. (Thien-3-yl)methylene Benzoxazinones (XXXIII).



XXXIII.

Table 45 lists the compounds synthesized having structural formula XXXIII. Examples 247-249 were synthesized as described in Example 236 using an appropriately substituted 2H-1,4-benzoxazin-3(4H)-one and an appropriately substituted thiophene-3-

carboxaldehyde. Examples 248 and 249 were then hydrogenated using the method described in Example 241 to form Examples 250 and 251.

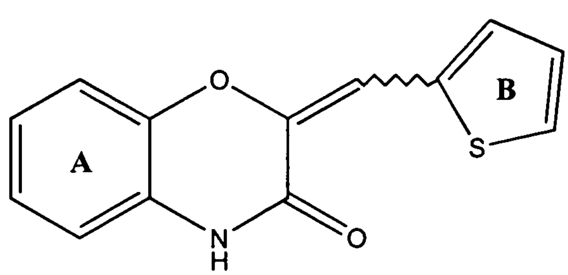
Table 45: Compounds synthesized having structural formula XXXIII.

Example	Substituent on Ring A	Substituent on Ring B	Recrystalization Solvent	% Yield	Method
247	none	none	acetonitrile	50	see Example 236
248	6-NO_2	none	DMF	55	see Example 236
249	7-NO_2	none	DMF	57	see Example 236
250	6-NH_2	none	ethanol	68	see Example 241
251	7-NH_2	none	ethanol	97	see Example 241

Table 46: Physical data for compounds synthesized having structural formula XXXIII.

Example	Mp. (°C)	Elemental analysis					
		Carbon		Hydrogen		Nitrogen	
		calculated	found	calculated	found	calculated	found
247	256-7	64.18	63.97	3.73	3.77	5.76	5.71
248	284-7	54.16	53.99	2.80	2.97	9.72	9.50
249	335-8	54.16	54.09	2.80	2.95	9.72	9.62
250	295-7	60.45	60.39	3.90	3.90	10.85	10.60
251	243-5	60.45	60.66	3.90	4.11	10.85	10.85

XXIV. (Thien-2-yl)methylene Benzoxazinones (XXXIV).



XXXIV.

Examples 252, 256 and 257 in Tables 47-52 were synthesized as described in Example 236 using an appropriately substituted 2H-1,4-benzoxazin-3(4H)-one and an appropriately substituted thiophene-2-carboxaldehyde, pyridine-3-carboxaldehyde, or *trans*-cinnamaldehyde. Example 252 was hydrogenated to form Example 253 using the reaction conditions described in Example 250.

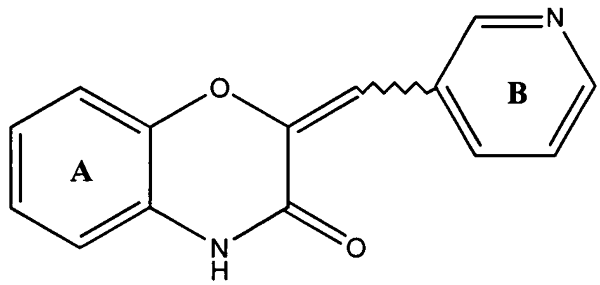
Table 47: Compounds synthesized having structural formula XXXIV.

Example	Substituent on Ring A	Substituent on Ring B	Recrystalization Solvent	% Yield	Method
252	7-NO_2	none	DMF	55	see Example 236
253	7-NH_2	none	ethanol	81	see Example 250
254	7-NH_2	3-CH_3	ethanol	90	see Example 241
255	7-NH_2	5-CH_3	ethanol	74	see Example 241

Table 48: Physical data for compounds synthesized having structural formula XXXIV.

Example	Mp. (°C)	Elemental analysis					
		Carbon		Hydrogen		Nitrogen	
		calculated	found	calculated	found	calculated	found
252	336-8	54.16	54.13	2.80	2.86	9.72	9.68
253	267-9	60.45	60.60	3.90	4.20	10.85	10.70
254	268-70	61.75	62.07	4.44	4.77	10.29	9.94
255	282-84	61.75	61.98	4.44	4.61	10.29	10.06

XXV. 2-[(Pyrid-3-yl)methylene]-2H-1,4-Benzoxazin-3(4H)-ones (XXXV).



XXXV.

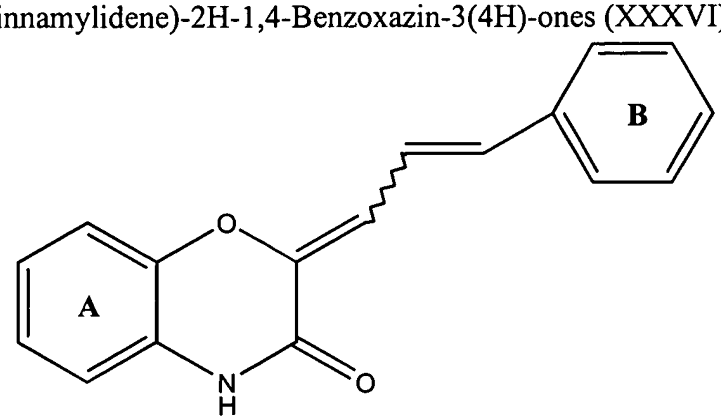
Table 49: Compounds synthesized having structural formula XXXV.

Example	Substituent on Ring A	Substituent on Ring B	Recrystalization Solvent	% Yield	Method
256	none	none	ethanol	34	see Example 236

Table 50: Physical data for compounds synthesized having structural formula XXXV.

Example	Mp. (°C)	Elemental analysis					
		Carbon		Hydrogen		Nitrogen	
		calculated	found	calculated	found	calculated	found
256	257-8	70.58	70.46	4.23	4.31	11.76	11.65

XXVI. 2-(Cinnamylidene)-2H-1,4-Benzoxazin-3(4H)-ones (XXXVI).



XXXVI.

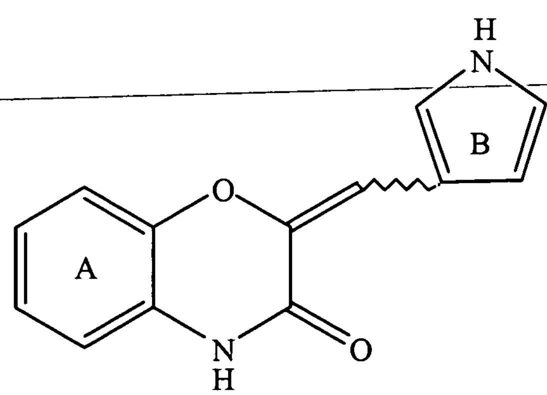
Table 51: Compounds synthesized having structural formula XXXVI.

Example	Substituent on Ring A	Substituent on Ring B	Recrystalization Solvent	% Yield	Method
257	none	none	DMF-acetonitrile	30	see Example 236

Table 52: Physical data for compounds synthesized having structural formula XXXVI.

Example	Mp. (°C)	Elemental analysis					
		Carbon		Hydrogen		Nitrogen	
		calculated	found	calculated	found	calculated	found
257	295-7	77.55	77.39	4.98	5.26	5.32	5.15

XXVII. (Pyrrol-3-yl)methylene Benzoxazinones (XXXVII).



XXXVII.

Example 258 was synthesized as described in Example 210 using an appropriately substituted 2H-1,4-benzoxazin-3(4H)-one and an appropriately substituted pyrrol-3-carboxaldehyde.

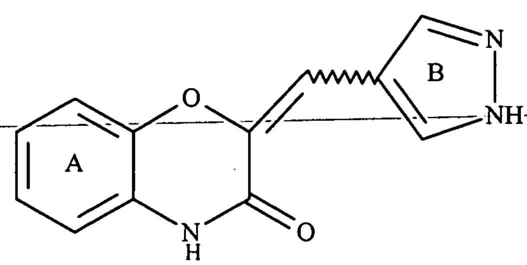
Table 53. Compounds synthesized having structural formula XXXVII.

Example	Substituent on Ring A	Substituent on Ring B	Chromatographic Mobile Phase	% Yield	Method
258	none	none	(95:5) to (90:10) toluene-ethyl acetate	15	see Example 210

Table 54. Physical data for compounds synthesized having structural formula XXXVII.

Example	Mp. (°C)	Elemental analysis					
		Carbon		Hydrogen		Nitrogen	
		calculated	found	calculated	found	calculated	found
258	240	69.02	68.69	4.59	4.42	12.21	12.30

XXVIII. (Pyrazol-4-yl)methylene Benzoxazinones (XXXVIII).



XXXVIII.

Example 259 from Table 55 was synthesized as described in Example 210. Examples 260-266 from Tables 55-58 were synthesized as described in Example 221 using an appropriately substituted 2H-1,4-benzoxazin-3(4H)-one and an appropriately substituted pyrazole-4-carboxaldehyde, imidazole-5-carboxaldehyde or imidazole-2-carboxaldehyde.

Table 55. Compounds synthesized having structural formula XXXVIII.

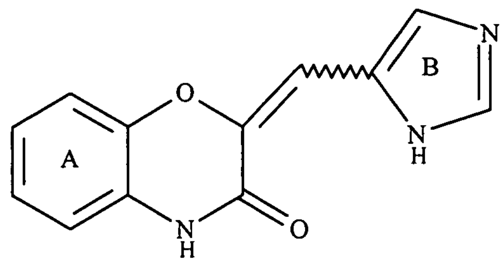
Example	Substituent on Ring A	Substituent on Ring B	Chromatographic Mobile Phase	% Yield (E)-isomer	% Yield (Z)-isomer	Method
259	none	3-CH_3	(50:50) ethyl acetate : dichlorometane	NA	20	see Example 210
260	none	3-CH_3	(50 : 50) to (30 : 70) dichloromethane : ethylacetate	66	12	see Example 221

Table 56. Physical data for compounds synthesized having structural formula XXXVIII.

Example	Mp. (°C)	Elemental analysis					
		Carbon		Hydrogen		Nitrogen	
		calculated	found	calculated	found	calculated	found
259 (Z)-isomer	323-5	64.72	64.48	4.59	4.66	17.41	17.20
260 (E)-isomer (0.5 C_2H_5OH)[1]	271-3	63.62	63.04	5.33	5.04	15.90	16.07
260 (Z)-isomer (0.2 C_2H_5OH)[1]	321-3	64.24	64.44	4.91	4.91	16.78	16.48

1) The molecular weight calculated for the elemental analysis includes the solvent in the amount indicated.

XXVIX. (Imidazol-5-yl)methylene Benzoxazinones (XXXIX).



XXXIX.

Example 261: Synthesis of (E)-2-[(Imidazol-5-yl)methylene]-2H-1,4-benzoxazin-3(4H)-one hydrochloride.

A solution 1 M of HCl in ethyl ether (7 ml) was dropwise to a mixture of (E)-2-[(imidazol-5-yl)methylene]-2H-1,4-benzoxazinone (0.76 g, 0.0033 mol) in dichloromethane : ethanol 2: 1 (120 ml). The reaction mixture was stirred at room temperature for 20 h. The precipitated solid was collected by filtration, washed with dichloromethane and dried. Yield 0.58 g (66%).

Table 57. Compounds synthesized having structural formula XXXIX.

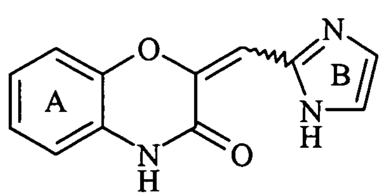
Example	Substituent on Ring A	Substituent on Ring B	Chromatographic Mobile Phase	% Yield (E)-isomer	% Yield (Z)-isomer	Method
261	none	none	(95 : 5) to (80 : 20) toluene : ethanol	70	17	see Example 221
261 (salt)	none	none	NA	66	-	see Example 261 (salt)
262	none	4-CH_3	(90 : 10) toluene : methanol	63	16	see Example 221
263	none	4-CH_2OH	NA	70	-	see Example 221
264	none	1-Methyl-2-methylthio	NA	64	-	see Example 221

Table 58. Physical data for compounds synthesized having structural formula XXXIX.

Example	Mp. (°C)	Elemental analysis					
		Carbon		Hydrogen		Nitrogen	
		calculated	found	calculated	found	calculated	found
261 (E)-isomer	272-4	63.43	63.23	3.99	4.06	18.49	18.20
261 (salt) (E)-isomer (0.3 H_2O)[1]	268-71	53.56	53.53	3.97	3.84	15.61	15.42
261 (Z)-isomer	>300	63.43	62.82	3.99	4.06	18.49	17.64
262 (E)-isomer (0.3 C_2H_5OH)[1]	275-7	63.93	63.54	5.13	4.80	16.33	16.40
262 (Z)-isomer (0.2 C_2H_5OH)[1]	297-300	64.26	63.79	4.91	4.98	16.78	16.55
263 (E)-isomer	262-4	15.77	15.88	4.61	4.43	60.40	60.04
264 (E)-isomer	247-9	58.52	58.57	4.56	4.80	14.62	14.64

1) The molecular weight calculated for the elemental analysis includes the solvent in the amount indicated.

XXX. (Imidazol-2-yl)methylene Benzoxazinones (XL).



XL.

Table 59. Compounds synthesized having structural formula XL.

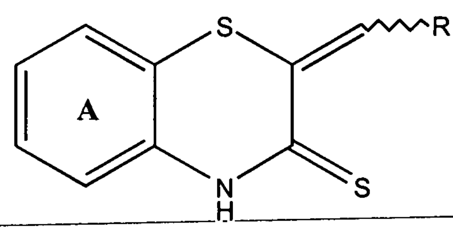
Example	Substituent on Ring A	Substituent on Ring B	Chromatographic Mobile Phase	% Yield (E)-isomer	% Yield (Z)-isomer	Method
265	none	none	(93 : 7) Toluene : ethanol	63	-	see Example 221
266	none	4-trifluoro methyl	(95 : 5) to (90 : 10) dichloromethane : ethylacetate to dichloromethane : ethanol	65	16	see Example 221
267	none	4-carboxy	NA	71	-	*

* This compound was obtained from the corresponding (imidazol-2-yl)methylene benzoxazinone already described by methods well known for those skilled in the art.

Table 60. Physical data for compounds synthesized having structural formula XL.

Example	Mp. (°C)	Elemental analysis					
		Carbon		Hydrogen		Nitrogen	
		calculated	found	calculated	found	calculated	found
265 (E)-isomer	304-6	63.43	63.03	3.99	4.01	18.49	18.28
266 (E)-isomer	290-2	52.89	52.59	2.73	2.98	14.23	13.90
266 (Z)-isomer	314-6	52.89	52.24	2.73	2.83	14.23	13.80
267 (Z)-isomer	>300	57.57	57.38	3.34	3.34	15.49	15.23

XXXI. Vinylidene Benzothiazine Thiones (XLI).



XLI.

Example 268: Synthesis of 2-[(Indol-3-yl)methylene]-2H-1,4-benzothiazine-3(4H)-thione:

A mixture of 2H-1,4-benzothiazin-3(4H)-thione (0.36 g, 2.0 mol), indole-3-carboxaldehyde (0.33 g, 2.3 mmol) and piperidine (3 drops) in dry ethanol (8 ml) was refluxed for 9 h. After cooling the precipitate was collected by filtration and the crude product was purified by recrystalization from toluene.

Examples 268-270 in Table 61 were synthesized as described in Example 268 using an appropriately substituted 2H-1,4-benzothiazin-3(4H)-thione and indole-3-carboxaldehyde, 7-azaindole-3-carboxaldehyde, or pyrrole-2-carboxaldehyde.

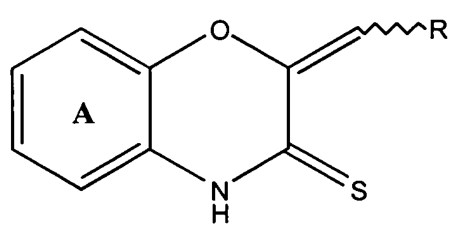
Table 61: Compounds synthesized having structural formula XLI.

Example	R	Recrystalization Solvent	% Yield	Method
268	Indol-3-yl	toluene	83	see Example 268
269	7-azaindol-3-yl	DMF-acetonitrile	87	see Example 268
270	Pyrrol-2-yl	ethyl acetate-hexane	64	see Example 268

Table 62: Physical data for compounds synthesized having structural formula XLI.

Example	Mp. (°C)	Elemental analysis					
		Carbon		Hydrogen		Nitrogen	
		calculated	found	calculated	found	calculated	found
268	253-6	66.20	66.16	3.92	4.01	9.08	8.96
269	287-90	62.11	61.88	3.58	3.91	13.58	13.57
270	205-6	60.44	60.23	3.90	3.92	10.84	10.71

XXXII. Vinylidene-Benzoxazine Thiones (XLII).



XLII.

Example 271: Synthesis of 2-[(Pyrrol-2-yl)methylene]-2H-1,4-benzoxazin-3(4H)-thione:

A mixture of 2H-1,4-benxoxazin-3(4H)-thione (0.33 g, 0.002 mol), pyrrole-2-carboxaldehyde (0.2 g, 0.021 mol) and 3 drops of piperidine in ethanol (14 ml) was refluxed for 3 h. The reaction mixture was cooled to room temperature and the

precipitated product was collected by filtration. The crude product was washed with ethanol, then purified by recrystalization from toluene.

Examples 271 and 272 in Table 63 were synthesized as described in Example 271 using 2H-1,4-benzothiazin-3(4H)-thione and indole-3-carboxaldehyde or pyrrole-2-carboxaldehyde.

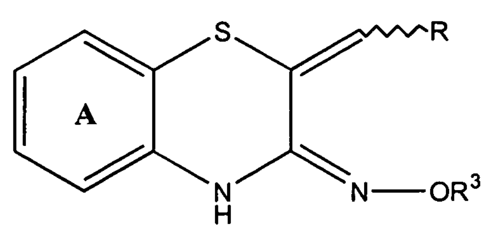
Table 63: Compounds synthesized having structural formula XLII.

Example	R	Recrystalization Solvent	% Yield	Method
271	Pyrrol-2-yl	Toluene	64	see Example 271
272	indol-3-yl	Ethanol	67	see Example 271

Table 64: Physical data for compounds synthesized having structural formula XLII.

Example	Mp. (°C)	Elemental analysis					
		Carbon		Hydrogen		Nitrogen	
		calculated	found	calculated	found	calculated	found
271	241-3	64.44	64.61	4.16	4.10	11.56	11.30
272	275-7	69.84	69.65	4.14	4.18	9.58	9.34

XXXIII. Imino Vinylidene Benzothiazines (XLIII).



XLIII.

Example 273: Synthesis of 3-Hydroxyimino-2-[(pyrrol-2-yl)methylene]-2H-1,4-benzothiazine:

A mixture of 2-[(pyrrol-2-yl)methylene]-2H-1,4-benzothiazine-3(4H)-thione (1.70 g, 6.6 mmol) (Example 270), hydroxylamine hydrochloride (1.38 g, 20.0 mmol) and triethylamine (2.18 g, 20.0 mmol) in dry ethanol (50 ml) was refluxed for 24 h with stirring. The solvent was removed *in vacuo* and the residue was purified by silica gel chromatography using (9 : 1) hexane : ethanol as the mobile phase.

Example 276: Synthesis of 3-Acetyloxyimino-2-[(pyrrol-2-yl)methylene]-2H-1,4-benzothiazine:

Acetic anhydride (1.3 ml, 13.78 mmol) was added to a solution of 3-hydroxyimino-2-[(pyrrol-2-yl)methylene]-2H-1,4-benzothiazine (0.27 g, 1.05 mmol) (Compound 273) in dry pyridine (1.5 ml). The reaction mixture was stirred for 30 minutes at room temperature, poured into ice water and extracted with ethyl acetate. The organic layer was washed with 10% HCl and brine, dried over magnesium sulfate and brought to dryness *in vacuo*. The residue was purified by silica gel chromatography using (9 : 1) dichloromethane : ethanol as the mobile phase.

Example 277: Synthesis of 3-Benzoyloxyimino-2-[(pyrrol-2-yl)methylene]-2H-1,4-benzothiazine:

A mixture of 3-hydroxyimino-2-[(pyrrol-2-yl)methylene]-2H-1,4-benzothiazine (0.28 g, 1.09 mmol) (Compound 273), benzoyl chloride (0.15 g, 1.09 mmol) and dry pyridine (2 drops) in dry toluene (5 ml) was stirred at room temperature for 4 hours. The precipitate was collected by filtration, washed with toluene, then purified by silica gel chromatography using (25 : 1) dichloromethane : ethyl acetate as the mobile phase.

Compounds 274 and 275 in Table 65 were synthesized as described in Example 273 except that 2-[(indol-3-yl)methylene]-2H-1,4-benzothiazine-3(4H)-thione (Compound 268) or 2-[(7-azaindol-3-yl)methylene]-2H-1,4-benzothiazine-3(4H)-thione (Compound 269) was substituted for 2-[(pyrrol-2-yl)methylene]-2H-1,4-benzothiazine-3(4H)-thione.

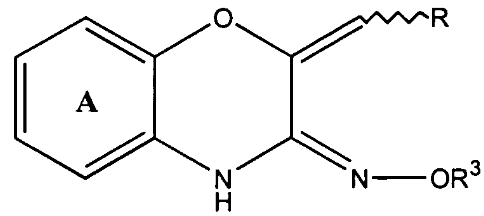
Table 65: Compounds synthesized having structural formula XLIII.

Example	R	R^3	Chromatographic Solvent	% Yield	Method
273	pyrrol-2-yl	H	(9 : 1) hexane : ethanol	55	see Example 273
274	indol-3-yl	H	(9 : 1) hexane : ethanol	18	see Example 273
275	7-azaindol-3-yl	H	(9 : 1) hexane : ethanol	10	see Example 273
276	pyrrol-2-yl	acetyl	(9 : 1) dichloromethane : ethanol	71	see Example 276
277	pyrrol-2-yl	benzoyl	(25 : 1) dichloromethane : ethyl acetate	46	see Example 277

Table 66: Physical data for compounds synthesized having structural formula XLIII.

Example	Mp. (°C)	Elemental analysis					
		Carbon		Hydrogen		Nitrogen	
		calculated	found	calculated	found	calculated	found
273	204-5	60.68	60.84	4.31	4.48	16.33	16.28
274	295-8	66.43	66.49	4.26	4.28	13.67	13.73
275	> 330	62.32	62.09	3.92	4.10	18.17	17.81
276	182-5	60.19	60.22	4.38	4.45	14.04	13.98
277	188-9	66.47	66.38	4.18	4.21	11.63	11.56

XXXIV. Imino Vinylidene Benzoxazines (XLIV).



XLIV.

Example 278: Synthesis of 3-Hydroxyimino-2-[(pyrrol-2-yl)methylene]-2H-1,4-benzoxazine:

A mixture of 2-[(pyrrol-2-yl)methylene]-2H-1,4-benzoxazin-3(4H)-thione (0.17 g, 0.7 mmol) (Example 271), hydroxylamine hydrochloride (0.45 g, 6.0 mmol) and triethylamine (0.6 ml, 6.0 mmol) in ethanol (10 ml) was refluxed for 6 h. The solvent was evaporated under reduced pressure, and the residue was stirred with ethyl acetate (30 ml) and filtered. The filtrate was evaporated to dryness to give the crude product which was purified by recrystalization from ethyl acetate : hexane.

Compound 279 in Table 67 was synthesized as described in Example 278 except that 2-[(indol-3-yl)methylene]-2H-1,4-benzoxazin-3(4H)-thione was substituted for 2-[(pyrrol-2-yl)methylene]-2H-1,4-benzoxazin-3(4H)-thione.

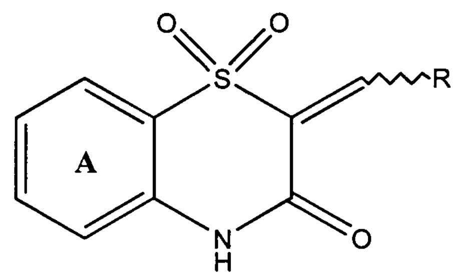
Table 67: Compounds synthesized having structural formula XLIV.

Example	R	R^3	Recrystalization Solvent	% Yield	Method
278	pyrrol-2-yl	H	ethyl acetate : hexane	65	see Example 278
279	indol-3-yl	H	ethyl acetate : hexane	84	see Example 278

Table 68: Physical data for compounds synthesized having structural formula XLIV.

Example	Mp. (°C)	Elemental analysis					
		Carbon		Hydrogen		Nitrogen	
		calculated	found	calculated	found	calculated	found
278	192-4	64.72	64.43	4.60	4.53	17.42	17.15
279	226-8	70.09	69.75	4.50	4.57	14.42	14.18

XXXV. 1,1-Dioxo Vinylidene Benzothiazinones (XLV).



XLV.

Example 280: Synthesis of 1,1-Dioxo-2-[(indol-3-yl)methylene]-2H-1,4-benzothiazin-3(4H)-one:

A mixture of 1,1-dioxo-2H-1,4-benzothiazin-3(4H)-one (0.59 g, 3.0 mmol), indole-3-carboxaldehyde (0.48 g, 3.3 mmol) and piperidine (3 drops) in anhydrous ethanol (6 ml) was refluxed for 17 h. After cooling to room temperature, the precipitate was collected by filtration and purified by recrystalization from ethyl acetate : hexane.

Compounds 281 and 282 in Table 69 were synthesized as described in Example 280 except that 7-azaindole-3-carboxaldehyde or pyrrole-2-carboxaldehyde was substituted for indole-3-carboxaldehyde.

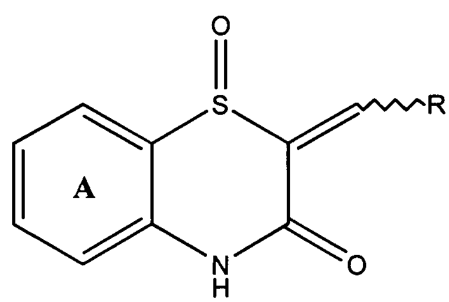
Table 69: Compounds synthesized having structural formula XLV.

Example	R	Recrystalization Solvent	% Yield	Method
280	indol-3-yl	ethyl acetate : hexane	94	see Example 280
281	7-azaindol-3-yl	DMF : H_2O	88	see Example 280
282	pyrrol-2-yl	ethanol	97	see Example 280

Table 70: Physical data for compounds synthesized having structural formula XLV.

Example	Mp. (°C)	Elemental analysis					
		Carbon		Hydrogen		Nitrogen	
		calculated	found	calculated	found	calculated	found
280	318-20	62.95	62.73	3.73	3.78	8.64	8.64
281	330-2	59.07	58.70	3.41	3.68	12.92	13.03
282	225-7	56.92	56.92	3.67	3.62	10.21	10.10

XXXVI. 1-Oxo-Vinylidene Benzothiazinones (XLVI).



XLVI.

Compound 283 in Table 71 was synthesized as described in Example 280 except that 1-oxo-2H-1,4-benzothiazin-3(4H)-one was used instead of 1,1-dioxo-2H-1,4-benzothiazin-3(4H)-one and 7-azaindole-3-carboxaldehyde was used instead of indole-3-carboxaldehyde. Compound 284 was synthesized as described in Example 280 except

that 1-oxo-2H-1,4-benzothiazin-3(4H)-one was used instead of 1,1-dioxo-2H-1,4-benzothiazin-3(4H)-one.

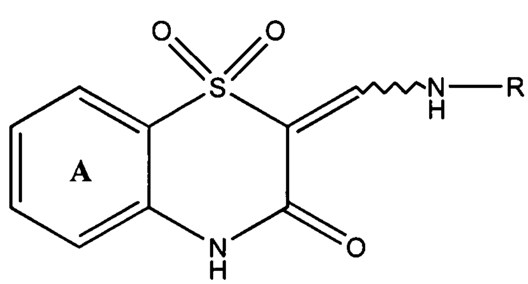
Table 71: Compounds synthesized having structural formula XLVI.

Example	R	Recrystalization Solvent	% Yield	Method
283	7-azaindol-3-yl	DMF : H_2O	63	see Example 280
284	indol-3-yl	NA	36	see Example 280

Table 72: Physical data for compounds synthesized having structural formula XLVI.

Example	Mp. (°C)	Elemental analysis					
		Carbon		Hydrogen		Nitrogen	
		calculated	found	calculated	found	calculated	found
283	292-4	62.12	61.91	3.58	3.70	13.58	13.43
284	276-8	66.22	65.82	3.92	4.02	9.08	8.98

XXXVII. 1,1-Dioxo Aminomethylene Benzothiazinones (XLVII).



XLVII.

Example 285: Synthesis of 1,1-Dioxo-2-[(4-methoxyphenylamino)methylene]-2H-1,4-benzothiazin-3(4H)-one:

A mixture of 1,1-dioxo-2-dimethylaminomethylene-2H-1,4-benzothiazin-3(4H)-one (0.25 g, 1.0 mmol) and 4-methoxyaniline (0.27 g, 2.2 mmol) in dry ethanol (20 ml)

was refluxed for 1 h. After cooling to room temperature, the precipitate was collected by filtration, washed with ethanol and purified by recrystalization using DMF : water.

Compounds 286-294 in Table 73 were synthesized using the method of Example 285 except 4-methoxyaniline was replaced by the appropriate amine .

Table 73: Compounds synthesized having structural formula XLVII.

Example	R	Recrystalization Solvent	% Yield	Method
285	4-methoxy-phenyl	DMF : H_2O	94	see Example 285
286	4-methyl-phenyl	DMF : H_2O	94	see Example 285
287	4-dimethyl-aminophenyl	DMF : H_2O	94	see Example 285
288	phenyl	DMF : H_2O	60	see Example 285
289	4-chlorophenyl	DMF : H_2O	78	see Example 285
290	pyrazol-3-ly	DMF : H_2O	69	see Example 285
291	1,2,4-triazol-3-yl	NA	34	see Example 285
292	indazol-5-yl	DMF : H_2O	82	see Example 285
293	pyrid-3-yl	NA	24	see Example 285
294	indol-5-yl	DMF : H_2O	82	see Example 285

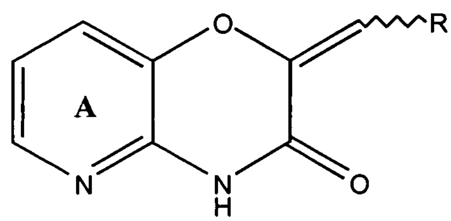
Table 74: Physical data for compounds synthesized having structural formula XLVII.

Example	Mp. (°C)	Elemental analysis					
		Carbon		Hydrogen		Nitrogen	
		calculated	found	calculated	found	calculated	found
285	250-1	58.17	58.14	4.27	4.34	8.48	8.51
286	264-6	61.13	61.12	4.49	4.37	8.91	9.02
287	278-80	59.46	59.48	4.99	4.78	12.24	12.34
288	255-6	59.99	59.96	4.03	4.03	9.33	9.44

289	299-300	53.82	53.72	3.31	3.12	8.37	8.36
290	298-300	49.65	49.83	3.47	3.60	19.30	19.23
291	307-9	45.36	45.51	3.11	3.17	24.04	23.90
292	320-3	56.46	56.09	3.55	3.62	16.46	16.30
293 (0.25 H_2O)[1]	285-6	54.98	55.00	3.79	3.74	13.74	13.56
294	268-70	60.17	59.85	3.86	4.06	12.38	12.34

1) The molecular weight calculated for the elemental analysis includes the solvent in the amount indicated.

XXXVIII. Vinylidene Pyridoxazinones (XLVIII).



XLVIII.

Example 295: Synthesis of 2-[(Pyrrol-2-yl)methylene]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one:

Sodium methoxide (0.65 g, 0.012 mol) was added in one portion to a mixture of 2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one (1.50 g, 0.01 mol) and pyrrole-2-carboxaldehyde (1.58 g, 0.016 mol) in dry DMF (10 ml). The reaction mixture was refuxed for 48 h, then cooled to room temperature, poured into crushed ice and left overnight at 4°C. The precipitated solid was filtered off, washed with water and dried. The dark solid was boiled with ethanol (150 ml) and filtered hot to remove impurities. The filtrate was evaporated to dryness under reduced pressure, and the residue was purified by silica gel chromatographed using (95 : 5) toluene : ethyl acetate as the mobile phase.

Example 297: Synthesis of 2-(Phenylmethylene)-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one:

Benzaldehyde (1.59 g, 0.016 mol) was added to a mixture of 2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one (1.50 g, 0.01 mol), acetic anhydride (4 ml) and triethylamine (2 ml). The reaction mixture was refluxed for 72 h, then cooled to room temperature. The precipitated solid was collected by filtration, washed with acetonitrile and purified by silica gel chromatography using (8 :2) toluene : ethyl acetate.

Compound 296 was synthesized using the method described in Example 295 except that indole-3-carboxaldehyde was substituted for pyrrole-2-carboxaldehyde.

Table 75: The following vinylidene pyridoxazinones (XLVIII) were synthesized.

Example	R	Chromatographic Solvent	% Yield	Method
295 (E)-isomer	pyrrol-2-yl	(95 : 5) toluene : ethyl acetate	2	see Example 295
295 (Z)-isomer	pyrrol-2-yl	(95 : 5) toluene : ethyl acetate	15	see Example 295
296	indol-3-yl	NA	20	see Example 295
297	phenyl	(8 : 2) toluene : ethyl acetate	12	see Example 297

Table 76: Physical data for compounds synthesized having structural formula XLVIII.

Example	Mp. (°C)	Elemental analysis					
		Carbon		Hydrogen		Nitrogen	
		calculated	found	calculated	found	calculated	found
295 (E)-isomer	254-5	63.43	63.55	3.99	4.12	18.49	18.20
295 (Z)-isomer	306-9	63.43	63.65	3.99	4.23	18.49	18.23

296	320-8	69.30	68.97	3.99	4.35	15.15	15.04
297	223-5	70.58	70.52	4.23	4.41	11.76	11.55

XXXIX. Synthesis of starting materials.

A. 1-substituted pyrrole-2-carboxaldehydes

Example 298: Synthesis of 1-(2-hydroxyethyl)-2-pyrrolcarboxaldehyde.

A solution of 2-pyrrolcarboxaldehyde (1.90 g, 0.02 m) in dry DMF (35 ml) was added dropwise, under nitrogen atmosphere, to a stirred suspension of 60% sodium hydride (oil dispersion) (0.96 g, 0.022 ml) in dry DMF (40 ml), keeping the temperature at 0°C. After addition was completed, stirring was continued at the same temperature for 30 min. Then a solution of 2-bromo ethylacetate (3.63 g, 0.022 m) in dry DMF (10 ml) was added dropwise and the temperature was allowed to rise to room temperature. The reaction mixture was stirred at this temperature fro 48 h. Then water (150 ml) was added and the mixture extracted with dichloromethane. The organic phase was dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure to give 1-(2-acetoxyethyl)-2-pyrrol carboxaldehyde as an oil. Sodium hydroxide (1.50 g) in water (37 ml) was added to a solution of this oil in methanol (50 ml) and the mixture was heated at 60°C for ½ hour. Solvent was removed and water (50 ml) was added. The mixture was extracted with ethyl acetate. The organic phase was dried and the solvent removed under reduced pressure to afford a red oil which was purified by column chromatography using toluene : ethanol 98 : 2 to 95 : 5 as eluent. Yield: 1.89 g (68%)

1-(4-hydroxybutyl)-2-pyrrolcarboxaldehyde was prepared following the same procedure described in example 298.

B. 1-substituted (7-aza)indole-3-carboxaldehydes.

Example 299: Synthesis of 1-benzoyloxyethyloxymethyl-7-azaindole-3-carboxaldehyde:

A solution of 7-azaindole-3-carboxaldehyde (2 g, 13.7 mmol) in dry N,N-dimethylformamide (30 ml) was added dropwise, under nitrogen atmosphere, to a stirring suspension of 60% sodium hydride (oil dispersion) (0.6 g, 15 mmol) in dry N,N-dimethylformamide (10 ml) keeping the temperature between 5-10°C (ice-water bath). After addition was completed, stirring was continued at the same temperature for 30 min. Then a solution of benzoyloxyethyl chloromethyl ether (3.8 g, 15 mmol) in dry N,N-dimethylformamide (40 ml) was added dropwise. After addition was complete, a catalytic amount of sodium iodide was added, and the temperature was allowed to rise to room temperature. The reaction mixture was allowed to stand at room temperature under nitrogen for 6 days, with intermittent stirring. Then water (100 ml) was added, and the mixture extracted with dichloromethane (3 x 100 ml). The organic phase was washed with water (100 ml), dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to give an oil (4.4 g, 99%), which was used without further purification.

Example 300: Synthesis of 1-Hydroxyethyloxymethyl-7-azaindole-3-carboxaldehyde:

A solution of sodium hydroxide (1.33 g, 33 mmol) in water (35 ml) was added to a solution of 1-benzoyloxyethyloxymethyl-7-azaindole-3-carboxaldehyde (5.4 g, 16 mmol) in methanol (45 ml). The mixture was heated at 60°C for 1 h, then the solvent was concentrated to half the original volume. Water was added, and the product was extracted with dichloromethane, dried over magnesium sulfate, filtered then evaporated to dryness. The product was used without further purification. Yield 2.7 g (74%)

Example 310: 1-(2,3-epoxypropyl)-indole-3-carboxaldehyde

Potassium hydroxide (0.38g, 6.9 mmol) was added to a stirred suspension of indole-3-carboxaldehyde (1 g; 6.9 mmol) in ethanol (100 ml). The mixture was stirred at room temperature for 15 min. The solvent was removed and the residue was treated with epichlorhydrin (4 ml) followed by heating at 100°C for 12 h. The mixture was then

allowed to cool, and the precipitated solid removed by filtration. The filtrate was evaporated under reduced pressure, and the residue chromatographed (silica gel, eluent toluene : ethanol 97:3) to yield 0.52 g (38%) of 1-(2,3-epoxypropyl)-indole-3-carboxaldehyde as an oil.

Example 311: 1-(2-hydroxy-N,N-dimethyl-3-aminopropyl)indole-3-carboxaldehyde

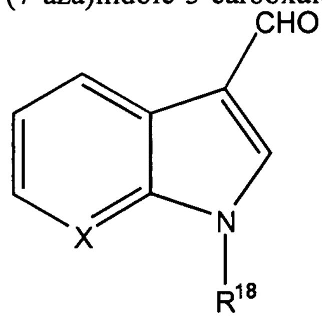
A mixture of 1-(2,3-epoxypropyl)indole-3-carboxaldehyde (0.5 g, 2.5 mmol), N,N-dimethylamine hydrochloride (4 g, 49 mmol) and anhydrous potassium hydroxide (2.75 g, 49 mmol) was stirred in dry methanol (50 ml) at -30°C for 8 h., then allowed to slowly warm to room temperature. The mixture was concentrated under reduced pressure to half the original volume, then water was added and the mixture was extracted with dichloromethane. After drying with anhydrous sodium sulfate the solvent was removed under reduced pressure, and the oily residue was chromatographed on a silica gel column (eluent dichloromethane:methanol from (9:1) to (8:2)) to yield the entitled product as a yellow oil 0.49 g (80%).

Example 318: 1-[3-Tetrahydrofuranyl]indole-3-carboxaldehyde

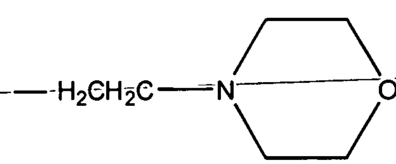
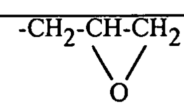
Indole-3-carboxaldehyde (0.72 g, 0.005 mol), 3-iodo tetrahydrofuran (0.99 g, 0.005 mol) and anhydrous potassium carbonate (0.69 g, 0.005 mol) in anhydrous N,N-dimethylformamide (7 ml) was stirred at 120°C for 6 h. The reaction mixture was filtered and the filtrate was evaporated to dryness. The residue was chromatographed on a silica gel column using toluene : ethyl acetate 95 : 5 as eluent to yield 0.15 g (14%) of the entitled product as an oil.

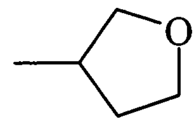
Aldehydes included in Table 77 were prepared following procedures described for compounds 299, 300, 310, 311 and 318 using the appropriate halogen derivative and the corresponding indole-3-carboxaldehyde or 7-azaindole-3-carboxaldehyde.

Table 77: 1-Substituted (7-aza)indole-3-carboxaldehydes synthesized.



XLIX.

Example	X	R^{18}
299	N	$-CH_2-O-CH_2-CH_2-OCOPh$
300	N	$-CH_2-O-CH_2-CH_2-OH$
301	CH	$-CH_2-O-CH_2-CH_2-OCOPh$
302	CH	$-CH_2-O-CH_2-CH_2-OH$
303	CH	$-CH_2-CH_2-CH_2-N(CH_3)_2$
304	N	$-CH_2-CH_2-CH_2-N(CH_3)_2$
305	N	
306	CH	$-CH_2-CH_2-CH_2-CH_2-OCOCH_3$
307	N	$-CH_2-CH_2-CH_2-CH_2-OCOCH_3$
308	CH	$-CH_2-CH_2-CH_2-CH_2-OH$
309	N	$-CH_2-CH_2-CH_2-CH_2-OH$
310	CH	
311	CH	$-CH_2-CH-CH_2-NMe_2$ OH
312	N	$-CH_2-CO_2CH_2CH_3$
313	CH	$-CH_2-CONH_2$
314	CH	$-CH_2-CH_2-CO_2CH_2CH_3$
315	CN	$-CO-N(CH_2CH_3)_2$

316	N	$-CH_2-O-CH_3$
317	N	$-CH_2-CH_2-N(CH_3)_2$
318	CH	

C. Indole-3-carboxaldehydes.

Example 319: Synthesis of 7-methoxycarbonyl-3-indolcarboxaldehyde:

To a stirred mixture of phosphorus oxychloride-dimethylformamide in anhydrous 1,2-dichloroethane (prepared by the slow addition of phosphorus oxychloride (0.43 ml, 4.6 mmol) to anhydrous DMF (0.35 ml, 4.6 mmol) in anhydrous 1,2-dichloroethane (6 ml) cooled below 5°C) a solution of 7-methoxycarbonylindole (0.69 g, 4 mmol) in anhydrous 1,2-dichloroethane (6 ml) was dropwise below 5°C. The mixture was stirred at room temperature for 2 h and then was heated at 50°C for 30 minutes. After cooling, the precipitate was filtered off and washed with 1,2-dichloroethane. This precipitate was suspended in aq Na_2CO_3 10% (30 ml) and stirred at room temperature for 20 minutes; dichloromethane was added and stirring was continued 10 minutes more. The organic phase was separated and the aqueous phase was extracted with dichloromethane. The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate and evaporated to yield 0.75 g (93%) of the entitled product. Mp: 153-4°C.

Example 320: Synthesis of 6-[(2-methoxyethyl)aminomethyl]indole-3-carboxaldehyde:

To a solution of 6-carboxyindole (1.5 g, 9.3 mmol) in dry N,N-dimethyl formamide (20 ml), 1,1'-carbonyldiimidazole (1.51 g, 9.3 mmol) was added under nitrogen atmosphere, and the mixture heated at 40°C for 1 h. Then 2-methoxyethylamine (1.39 g, 18.0 mmol) was added and the mixture heated at the same temperature for an additional time of 20 h. The solvent was removed under reduced pressure and the residue treated with water and extracted with dichloromethane. The organic layer was dried over

anhydrous sodium sulfate. Filtration and elimination of the solvent under reduced pressure gave an oil which was identified as 6-[N-(2-methoxyethyl)carbamoyl]indole, and used without further purification in the next step.

To a suspension of lithium aluminum hydride (0.93 g, 24.5 mmol) in anhydrous tetrahydrofurane (15 ml), aluminum trichloride (3.5 g, 24.5 mmol) was added portionwise at 0°C for 30 min and then 6-[N-(2-methoxyethyl)carbamoyl] indole (1 g, 4.5 mmol) was added portionwise at 0°C for 1 h. After stirring overnight at room temperature, the reaction mixture was quenched with 20% NaOH while cooling in ice water. The precipitate was filtered and washed with dichloromethane and the solvent evaporated after dried over anhydrous sodium sulfate. The residue was chromatographed on silica gel (eluent, dichloromethane : methanol, 9 : 1) and then the product was precipitated with hexane to give 0.3 g (32%) of 6-[(2-methoxyethyl)aminomethyl]indole

To a stirred mixture of phosphorous oxychloride-dimethylformamide in anhydrous 1,2-dichloroetane, prepared by the slow addition of phosphorous oxychloride (0.25 ml, 2.7 mmol) to anhydrous DMF (0.19 ml, 2.9 mmol) in 1,2-dichloroethane (5 ml) cooled below 5°C, a solution of 6-[(2-methoxyethyl) aminomethyl]indole (0.5 g, 2.5 mmol) in anhydrous 1,2-dichloroethane (5 ml) was added dropwise below 5°C. The mixture was stirred at room temperature for 24 h. Then, water and 10% sodium hydroxide were added to pH = 9. The mixture was extracted with dichloromethane and the pH of the aqueous layer adjusted to pH = 7 with 10% HCl. The mixture was evaporated to dryness under reduced pressure and the residue extracted with methanol. The precipitate was filtered off and the solvent removed. The resulting oily residue containing the required product was used without further purification.

Compound 6-[(3-dimethylaminopropyl)aminomethyl]indole-3-carboxaldehyde was prepared by a procedure similar to the one described for 6-[(2-methoxyethyl)aminomethyl]indole-3-carboxaldehyde.

Example 321: Synthesis of 5-acetaminomethylindole-3-carboxaldehyde:

5-Aminomethylindole (5.3 g, 0.036 mol) was mixed with acetic anhydride (13 ml) and kept at room temperature for 3 h. The solvent was removed under reduced pressure and the residue was stirred with toluene. The precipitated solid was collected by filtration to yield 6.1 g (89%) of 5-acetaminomethylindole.

Phosphorus oxychloride (0.38 ml, 0.004 mol) was slowly added at 0°C under nitrogen atmosphere to anhydrous N,N-dimethylformamide (1.9 ml, 0.025 mol). The mixture was stirred for 15 minutes and a solution of 5-acetamino methylindole (0.73 g, 0.0039 mol) in anhydrous N,N-dimethylformamide (4 ml) was added dropwise below 2°C. The mixture was stirred at room temperature for 3 h and diluted with an equal volume of water. The solution was neutralized (pH 8) with 1 N aqueous solution of sodium hydroxide. The mixture was evaporated to dryness under reduced pressure and the residue was recrystallized from ethyl acetate to afford 0.5 g (60%) of the entitled product (mp 182-184°C).

Example 322: Synthesis of 6-(N,N-dimethylaminosulfonyl)indole-3-carboxaldehyde:

Phosphorus oxychloride (0.76 ml, 0.008 mol) was slowly added at 0°C under nitrogen atmosphere to anhydrous N,N-dimethyl formamide (3.8 ml), 0.05 mol). The mixture was stirred for 15 minutes and a solution of 6-(N,N-dimethyl aminosulfonyl)indole (1.74 g, 0.0078 mol) in anhydrous N,N-dimethylformamide (4 ml) was added dropwise below 2°C. The reaction mixture was allowed to stand at room temperature for 20 h and diluted with water (10 ml). The solution was neutralized (pH 8) with 10% aqueous solution of sodium hydroxide. The mixture was cooled and the precipitated solid was collected by filtration and was recrystallized from ethanol to yield 1.05 g (54%) of the entitled product (mp 250-252°C).

Example 323: 8-(Acetoxymethyl)-6,7,8,9-tetrahydro-pyrido[1,2-a]-indole-10-carboxaldehyde:

Phosphorus oxychloride (0.76 ml, 0.008 mol) was slowly added at 0°C under nitrogen atmosphere to anhydrous N,N-dimethylformamide (3.8 ml, 0.05 mol). The mixture was stirred for 15 minutes and a solution of 8-(acetoxymethyl)-6,7,8,9-tetrahydro-pyrido[1,2-a]indole (1.9 g, 0.0078 mol) in anhydrous N,N-dimethyl formamide (19 ml) was added dropwise below 2°C. The mixture was stirred at 0°C for 2 h, poured into crushed ice and the solution was neutralized (pH 8) with 10% aqueous solution of sodium hydroxide and the mixture was extracted with ethyl acetate, washed with water, 10% aqueous sodium hydrogencarbonate solution and water. The organic solvent was dried over anhydrous magnesium sulfate to yield 1.77 g (84%) of the entitled product (mp 118-120°C).

D. Imidazole-5-carboxaldehydes.

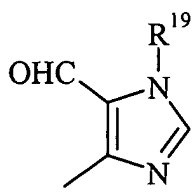
Example 324: Synthesis of a mixture of 1-(N,N-diethyl-2-aminoethyl)-4(5)-methylimidazole-5(4)-carboxaldehydes:

A solution of 4(5)-methylimidazole-5(4)-carboxaldehyde (1 g, 9.09 mmol) in dry N,N-dimethylformamide (30 ml) was added dropwise under nitrogen atmosphere to a stirring suspension of 60% sodium hydride (oil dispersion) (0.73 g, 18.16 mmol) in dry N,N-dimethylformamide (10 ml) keeping the temperature between 5-10°C (ice-water bath). After addition was completed, stirring was continued at the same temperature for 30 min. Then a solution of N,N-diethyl aminoethyl chloride hydrochloride in dry N,N-dimethylformamide (20 ml) was added dropwise. After that a catalytic amount of sodium iodide was added, and the temperature was allowed to rise to room temperature. The reaction mixture was stirred for 2 days. Water (50 ml) was added and the mixture extracted with dichloromethane (3 x 50 ml). The organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to give an

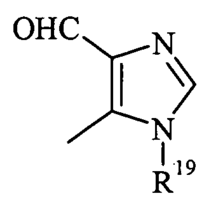
oil containing a mixture of the entitled compounds (1 g, 52%) which was used without further purification.

Example 325 was prepared following the procedure described for example 324 using the appropriate halogen derivative and 4(5)-methylimididazole-5(4)-carboxaldehyde.

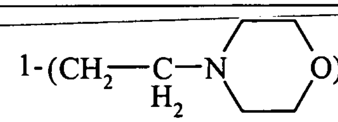
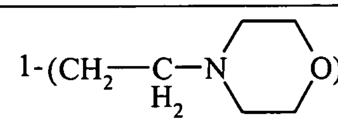
Table 78. N-substituted 4(5)-methylimidazole-5(4)-carboxaldehydes synthesized.



L.



LI.

Example	Structure number	R^{19}
324	L	1-[CH_2-CH_2-N(CH_2-CH_3)$_2$]
324	LI	1-[CH_2-CH_2-N(CH_2-CH_3)$_2$]
325	L	
325	LI	

Example 326: Synthesis of 4(5)-hydroxymethylimidazole-5(4)-carboxaldehyde:

4(5)-Diethoxymethyl-5(4)-methoxycarbonylimidazole (0.75 g, 0.0033 mol) was added portionwise with ice cooling under nitrogen atmosphere to a stirred suspension of lithium aluminum hydride (0.33 g, 0.0088 mol) in anhydrous tetrahydrofurane (40 ml). The mixture was stirred at room temperature for 3 hr and quenched by cautious addition of saturated aqueous of sodium sulfate. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure, to yield 0.46 g (65%) of 4(5)-diethoxymethyl-

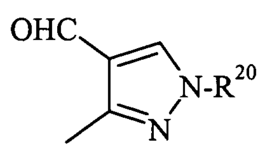
5(4)-hydroxymethylimidazole, which was used without further purification in the next step

4(5)-Diethoxymethyl-5(4)-hydroxymethylimidazole (0.23 g, 0.0011 mol) was stirred with acetic acid/water (8 ml/2ml) at room temperature for 2 hr. The reaction mixture was evaporated to dryness to yield 0.13 g (95%) of the entitled product, mp 160-162°C.

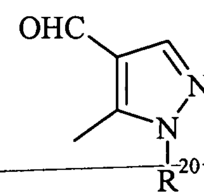
E. Pyrazole-4-carboxaldehydes.

Aldehydes included in Table 79 were prepared following the procedure described for example 324 using the appropriate halogen derivative and 3-methylpyrazole-4-carboxaldehyde.

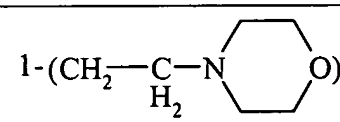
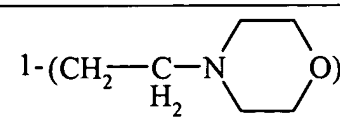
Table 79. N-substituted 3-methylpyrazole-4-carboxaldehydes synthesized.



LII.



LIII.

Example	Structure number	R^{20}
327	LII	1-[CH_2-CH_2-N(CH_2-CH_3)$_2$]
327	LIII	1-[CH_2-CH_2-N(CH_2-CH_3)$_2$]
328	LII	
328	LIII	
329	LII	1-(CH_2-$CO_2CH_2CH_3$)
329	LIII	1-(CH_2-$CO_2CH_2CH_3$)

F. Indole-7-carboxaldehydes and Indole-4-carboxaldehydes.

Example 330: Synthesis of 3-dimethylaminomethyl-7-indolcarboxaldehyde:

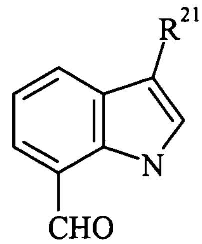
A mixture of 7-indolcarboxaldehyde (0.25 g, 1.7 mmol) and Eschenmoser's salt (0.35 g, 1.9 mmol) in dry acetonitrile (10 ml) was heated under reflux for 2½ h. After cooling, solvent was removed under reduced pressure and water was added to the residue. The cooled mixture (ice bath) was made alkaline with 10% sodium hydroxide and then extracted with dichloromethane. The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate and evaporated to afford 0.25 g (74%) of the entitled product.

Example 331: Synthesis of 3-morpholinomethyl-4-indolcarboxaldehyde:

Morpholine (0.24 ml, 2.7 mmol) and formaldehyde (37% aq; 0.21 ml, 2.7 mmol) were added to glacial acetic acid (3 ml) at 0°C. After stirring for 15 minutes 4-indolcarboxaldehyde (0.27 g, 1.9 mmol) was added. The mixture was stirred 5 minutes at 0°C and then 3½ h at room temperature, prior to the addition of water (6 ml) and washing with ether. The aqueous layer was made alkaline with 2N NaOH and then extracted with dichloromethane. The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate and evaporated to afford 0.46 g of the entitled product as an oil which was used without further purification.

Aldehydes included in Table 80 were prepared following the procedures described for compounds 330 and 331.

Table 80. Indole-7-carboxaldehydes synthesized.



Example	R^{21}	Mp (°C)	Yield %
330	dimethylaminomethyl	205-7	74
332	morpholinomethyl	148-50	86
333	piperidinomethyl	84-7	100
334	(4-methylpiperazin-1-yl)methyl	NA (oil)	93
335	[4-(2-hydroxyethyl)piperazin-1-yl]methyl	87-90	93

G. Example 136: Synthesis of 6-Cyano-2H-1,4-Benzoxazin-3(4H)-one:

Chloroacetyl chloride (3.12 ml, 38 mmol) was added dropwise to a solution of 2-amino-4-cyanophenol (4.96 g, 37 mmol), triethylamine (10.98 ml, 78 mmol) and 4-(dimethylamino)pyridine (0.09 g, 0.74 mmol) in dry dichloromethane (40 ml) maintained at 0°C. The solution refluxed for 24 h. The reaction mixture was cooled, and the organic layer was washed with phosphoric acid (0.5 M), saturated sodium bicarbonate, water and brine, then dried with anhydrous magnesium sulfate. The organic layer was filtered, then evaporated to dryness. The residue was recrystalized from ethanol to afford 3.9 g (60%) of the titled compound. (mp 243-245°C).

H. Synthesis of 2H-1,4-Benzothiazin-3-ones.

Example 337: Synthesis of 1-Oxo-2H-1,4-Benzothiazin-3(4H)-one

A solution of 3-chloroperbenzoic acid (1.35 g, 6.6 mmol) in dry dichloromethane (40 ml) was added dropwise to an ice cooled solution of 2H-1,4-benzothiazin-3(4H)-one (1.10 g, 6.6 mmol) in dry dichloromethane (100 ml) with stirring. The reaction mixture was allowed to reach room temperature, then stirred overnight. The product was collected by filtration and washed with dichloromethane. Yield 0.54 g (45%) mp 184-6°C

Example 338: Synthesis of 7-(N,N-Dimethyl-3-aminopropyloxy)-2H-1,4-benzothiazin-3(4H)-one.

N,N-dimethyl-3-aminopropanol (0.27 g, 5.2 mmol) was added to a mixture of 7-hydroxy-2H-1,4-benzothiazin-3(4H)-one (0.95 g, 5.2 mmol) and triphenylphosphine (1.37 g, 5.2 mmol) in dry tetrahydrofurane (30 ml) under nitrogen atmosphere, followed by diethyl azodicarboxylate (1 g, 5.7 mmol). The mixture was stirred at room temperature for 48 h, concentrated *in vacuo*, and the product was purified by silica gel chromatography using dichloromethane:methanol gradient of (9 : 1) to (7 : 3) as the mobile phase. Yield 1.1 g (75%) mp 120-121°C

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the spirit and scope of the invention as defined by the appended claims.